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Investigation of the correlation between neurocognitive function with advanced magnetic resonance imaging (MRI), electroencephalography (EEG) in patients with traumatic brain injury exposure

Neurocognitive function and advanced MRI and EEG

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In conducting the research described in this report, the investigators adhered to the policies and procedures set out in the Tri-Council Policy Statement: Ethical conduct for research involving humans, National Council on Ethics in Human Research, Ottawa, 1998 as issued jointly by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada.

Abstract

Introduction: In the Canadian Forces (CF), injuries involving impact of the head within an enclosed space (a vehicle) are common and the possibility of cortical impact injuries in such cases is quite high. While conventional neuroimaging techniques may show normal results, cognitive problems are frequently reported by people who have sustained cortical impact or traumatic brain injury. In order to develop a comprehensive clinical diagnosis for return soldiers that might experience signs and symptoms of possible brain injury due to cortical impact, the present study aimed to compare motor vehicle accident (MVA) victims where cortical impact is prevalent to an age matched control group. All MVA victims were investigated using carefully selected neuroimaging and electrophysiological procedures together with a validated neurocognitive test battery. **Results:** 1) at the neuropsychological level, postconcussive symptoms (PCS) were the most notable complaints expressed by almost all patients; followed by symptoms of depression and anxiety. The majority of patients showed at least one motor deficit while the rest of their profile was mixed underlining differential effects on cognitive functions. There were no verbal memory deficits while the majority of MVA subjects showed problems with at least one visuospatial memory task; 2) with functional magnetic resonance imaging the results were consistent with our previous work. The presence and severity of PCS were associated with reduced BOLD activation in dorsolateral prefrontal cortex (DLPFC). Similarly, the presence and severity of symptoms of depression were associated with reduced deactivation in rostral anterior cingulate cortec (rACC) and medial orbitofrontal cortex (mOFC). This pattern is in line with the fact that those depressed subjects who did not show this profile were on antidepressant medication at the time of the study. Atypical findings were also noted in three healthy subjects highlighting the importance of building a solid normal control database with a reliable sample size in order to establish the normal range of brain activation magnitude in the regions of interests; 3) with event-related potentials (ERP), MVA victims presented lower P300 amplitudes and a smaller N350 than the control subjects, in keeping with the presence of attentional dysfunctions. In addition, quasi normal behavioural results in the MVA group was observed suggesting use of cerebral compensatory mechanisms by that group. **Conclusion:** In MVA victims, PCS are associated with cognitive dysfunctions that vary among individuals and this underscores the necessity of using an exhaustive neuropsychological test battery with this population. PCS appear to have a pathological basis as they are associated with cerebral dysfunctions, particularly in frontal, parietal, and hippocampal regions, identified with event-related potentials and functional neuroimaging. As conventional neuroimaging (e.g. CT, MRI) does not allow identification of dysfunctional regions, the evaluation of the severity of PCS, including depression and anxiety, following a MVA is primordial as it has implications for diagnosis, treatment, and rehabilitation. Our approach, using neuropsychological testing, fMRI and ERP, holds great potential for identifying the presence of suspected cerebral dysfunctions in soldiers following traumatic brain injury, particularly in blast exposure.

Résumé

Introduction: Au sein des Forces Armées Canadiennes, les blessures impliquant un impact à la tête dans un environnement restreint comme celui dans un véhicule motorisé sont communes et la possibilité que les passagers y subissent un traumatisme crânio-cérébral (TCC) est très élevée.

Alors que les méthodes conventionnelles d'imagerie cérébrale montrent habituellement des résultats normaux, des problèmes cognitifs sont souvent rapportés par les victimes de TCC. Afin de développer une batterie clinique diagnostique applicable aux soldats se plaignant de symptômes laissant présager la présence d'un TCC suite à une exposition à une explosion, la présente étude visait à comparer des accidentés de la route chez qui un TCC prévaut à un groupe témoin pairé selon l'âge. Tous les sujets TCC ont été soumis à une batterie de tests neuropsychologiques, d'imagerie cérébrale fonctionnelle et électrophysiologiques. **Résultats:** 1) **au plan neuropsychologique**, les symptômes post-commotionnels (SPC) prévalaient chez les sujets TCC suivis de symptômes de dépression et d'anxiété. La majorité des patients ont montré au moins un déficit moteur alors que le reste de leur profil était mixte soulignant des effets différentiels sur le fonctionnement cognitif. Aucun déficit des fonctions verbales n'a été constaté mais la majorité des TCC ont montré des difficultés lors d'au moins une tâche de mémoire visuelle. 2) avec **la résonance magnétique fonctionnelle**, les résultats étaient généralement en accord avec ceux obtenus lors de nos études précédentes. La présence et la sévérité des SPC étaient associées avec un signal en oxygénation sanguine (BOLD) réduit dans le cortex dorso latéral préfrontal. De façon analogue, la présence et la sévérité des symptômes dépressifs étaient associées avec une désactivation réduite dans le cortex cingulaire antérieur rostral et dans le cortex orbitofrontal médian. Ces résultats s'enlignent avec le fait que les sujets se plaignant de symptômes dépressifs ne montrant pas ce patron d'activation prenaient de la médication antidépressive au moment de l'étude. Des résultats atypiques ont également été obtenus par trois sujets témoins, ce qui souligne l'importance de cumuler des données normatives solides avec un échantillonnage fiable. 3) avec **les potentiels évoqués**, les TCC ont montré des amplitudes réduites des ondes P300 et N350 par rapport aux sujets témoins, en accord avec la présence de dysfonctions attentionnelles chez le groupe TCC. De plus, les performances comportementales quasi normales observées chez les TCC laissent croire à l'utilisation de mécanismes cérébraux compensatoires par ce groupe. **Conclusions :** Chez les TCC, les SPC sont associés à des dysfonctions cognitives variables selon les individus et ceci souligne la nécessité d'utiliser une batterie neuropsychologique exhaustive chez cette population. Les SPC semblent avoir une pathologie sous-jacente car ils sont associés à des dysfonctions cérébrales touchant particulièrement les régions frontale, pariétale et hippocampique identifiées par l'imagerie cérébrale fonctionnelle et les potentiels évoqués. Étant donné que l'imagerie cérébrale conventionnelle (par ex. CT scan, IRM) ne permet pas d'identifier des régions dysfonctionnelles, l'évaluation de la sévérité des SPC, incluant la dépression et l'anxiété, à la suite d''un accident de la route ou à l'exposition à une explosion, revêt une importance primordiale à cause des implications qu'elle a pour le diagnostic, le traitement et la réadaptation. Notre approche utilisant la résonance magnétique fonctionnelle, l'évaluation neuropsychologique et les potentiels évoqués possède un potentiel considérable pour identifier la présence possible de dysfonctions cérébrales suite à un TCC particulièrement lors de l'exposition à une explosion

Executive summary

Investigation of the correlation between neurocognitive function with advanced magnetic resonance imaging (MRI), electroencephalography (EEG) in patients with traumatic brain injury exposure: Neurocognitive function and advanced MRI and EEG

A. Ptito, B. Cheung, J.-K. Chen, N. Gosselin, S. Huntgeburth, G. Leonard, M. Petrides; DRDC Toronto CR 2011-015; Defence R&D Canada – Toronto; January 2011.

Introduction or background: In the Canadian Forces (CF), impact to the head within an enclosed space (a vehicle) is common and the possibility of injuries to the brain in such cases is quite high. A mild traumatic brain injury (MTBI) is the acute consequence of blunt impact or other mechanical energy, such as sudden acceleration, deceleration or rotation, to the head from external forces. Persisting symptoms that can include headache, sleep disturbance, disorders of balance, cognitive impairments, fatigue, and mood or affective disorders are common after MTBI and up to 20% of individuals continue to experience significant symptoms beyond the normal recovery period. While some MTBI's cause visible structural damage, the majority results mainly in functional disturbances that may be due to microscopic damage that is difficult to measure in a patient. This type of damage cannot be detected by conventional neuroimaging such as CT and MRI but functional MRI (fMRI) can be used in MTBI victims to measure normal or abnormal increases in blood flow in the regions of the brain that are involved in a task. Similarly, event related potentials or ERP can be used to measure the normal or abnormal electrical activity of certain brain regions associated with a task. In order to develop clinical diagnostic tools for return soldiers that might experience signs and symptoms of possible brain injury due to cortical impact, the present study compared motor vehicle accident (MVA) victims where cortical impact is prevalent to an age matched control group. All the subjects were investigated using carefully selected neuroimaging and electrophysiological procedures together with a validated cognitive test battery.

Results: Cognitive: almost all patients complained of post concussive symptoms (PCS) such as headaches, depression and anxiety and they showed at least one motor deficit. The rest of their cognitive profile was mixed indicating that cognitive dysfunctions following MTBI vary from one individual to another. There were no verbal memory deficits but the majority of patients showed problems with at least one visuospatial memory task such as recalling a complex geometric figure they had copied adequately previously; 2) Functional magnetic resonance imaging: consistent with our previous work, presence and severity of PCS were associated with reduced activation in frontal regions of the brain. Similarly, the presence and severity of symptoms of depression correlated with a pattern of brain activity resembling that of patients with major depression. We noted that those depressed patients with MTBI who did not show this cerebral profile were on antidepressant medication at the time of the study; 3) Event-related potentials or ERP: continuous electrical activity of the brain was recorded during the same visual memory task as the one used with fMRI. MVA victims presented lower electrical activity in parietal (attentional processes) and frontal (working memory processes) brain areas than the control subjects.

Future plans: In MVA victims, PCS are associated with cognitive dysfunctions that vary among individuals and this underscores the necessity of using an exhaustive neuropsychological test battery with this population. PCS appear to be associated with cerebral dysfunctions, particularly in frontal and parietal regions of the brain, identified with event-related potentials and functional neuroimaging. As conventional neuroimaging (e.g. CT, MRI) does not allow identification of dysfunctional regions, the evaluation of the severity of PCS, including depression and anxiety, following a MVA or blast exposure is essential as it has implications for diagnosis, treatment, and rehabilitation. Our approach, using neuropsychological testing, fMRI and ERP, holds great potential for identifying the presence of suspected cerebral dysfunctions in soldiers following traumatic brain injury, particularly in blast exposure.

Sommaire

Investigation of the correlation between neurocognitive function with advanced magnetic resonance imaging (MRI), electroencephalography (EEG) in patients with traumatic brain injury exposure: Neurocognitive function and advanced MRI and EEG

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Introduction ou contexte: Au sein des Forces Armées Canadiennes, les blessures impliquant un impact à la tête dans un environnement restreint comme celui dans un véhicule motorisé sont communes et la possibilité que les passagers y subissent un traumatisme crânio-cérébral (TCC) est très élevée. Un TCC léger résulte d'un choc brutal, tel une accélération, décélération ou rotation soudaine, à la tête engendré par des forces externes. Des symptômes persistants tels que maux de tête, troubles du sommeil, problèmes d'équilibre, déficits cognitifs, fatigue et troubles de l'humeur ou affectifs sont communs suite à un TCC et jusqu'a 20% des individus continuent de se plaindre de symptômes après la période de recouvrement normale. Alors que certains TCC causent des dommages cérébraux visibles, la majorité entraine des troubles plutôt fonctionnels qui peuvent être associés à des lésions microscopiques difficiles à mesurer. Ce type de dommage ne peut être détecté par les méthodes conventionnelles d'imagerie cérébrale telles que la tomodensitométrie ou la résonance magnétique mais la résonance magnétique fonctionnelle peut être utilisée chez les victimes d'un TCC léger pour mesurer les augmentations normales et anormales en flux sanguin dans des régions cérébrales spécifiques associées à l'accomplissement d'une tache. De façon similaire, les potentiels évoqués peuvent être utilisés pour mesurer l'activité électrique normale ou anormale dans ces régions avec les mêmes taches. Afin de développer une batterie clinique diagnostique applicable aux soldats se plaignant de symptômes laissant présager la présence d'un TCC suite à une exposition à une explosion, la présente étude visait à comparer des accidentés de la route chez qui un TCC prévaut à un groupe témoin pairé selon l'âge. Tous les sujets ont été soumis à une batterie de tests neuropsychologiques standardisés, d'imagerie cérébrale fonctionnelle et de potentiels évoqués

Résultats: 1) **au plan neuropsychologique**, presque tous les patients se plaignaient de symptômes post-commotionnels (SPC) tels que maux de tête, dépression et anxiété et montraient au moins un déficit moteur. Le reste de leur profil était mixte soulignant que les dysfonctions cognitives suite à un TCC varient d'un individu à l'autre. Aucun déficit des fonctions verbales n'a été constaté mais la majorité des TCC ont montré des difficultés lors d'au moins une tâche de mémoire visuelle telle qu'évoquer en rappel différé une figure géométrique complexe qu'ils avaient copié adéquatement auparavant; 2) avec **la résonance magnétique fonctionnelle**, les résultats étaient généralement en accord avec ceux obtenus lors de nos études précédentes. La présence et la sévérité des SPC étaient associées à une activation réduite dans les régions frontales du cerveau. De façon analogue, la présence et la sévérité des symptômes dépressifs étaient associées à un patron d'activité cérébrale similaire à celui de patients souffrant de dépression majeure. A cet effet, les patients se plaignant de symptômes dépressifs ne montrant pas ce patron d'activation étaient sous médication antidépressive au moment de l'étude; 3) avec **les potentiels évoqués**, l'activité électrique cérébrale a été enregistrée continuellement pendant l'accomplissement de la même tache de mémoire visuelle que celle utilisée lors de l'étude par

résonance magnétique fonctionnelle. Les TCC ont montré une activité électrique réduite dans les régions pariétale (fonctions attentionnelles) et frontale (mémoire de travail) par rapport aux sujets témoins.

Perspectives: Chez les TCC, les SPC sont associés à des dysfonctions cognitives variables selon les individus et ceci souligne la nécessité d'utiliser une batterie neuropsychologique exhaustive chez cette population. Les SPC semblent avoir une pathologie sous-jacente car ils sont associés à des dysfonctions cérébrales touchant particulièrement les régions frontale et pariétale du cerveau, identifiées par l'imagerie cérébrale fonctionnelle et les potentiels évoqués. Étant donné que l'imagerie cérébrale conventionnelle (par ex. CT scan, IRM) ne permet pas d'identifier des régions dysfonctionnelles, l'évaluation de la sévérité des SPC, incluant la dépression et l'anxiété, à la suite d''un accident de la route ou à l'exposition à une explosion, revêt une importance primordiale à cause des implications qu'elle a pour le diagnostic, le traitement et la réadaptation. Notre approche utilisant la résonance magnétique fonctionnelle, l'évaluation neuropsychologique et les potentiels évoqués possède un potentiel considérable pour identifier la présence possible de dysfonctions cérébrales suite à un TCC particulièrement lors de l'exposition à une explosion.

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1 Introduction

Despite aggressive protective measures and safety practices, blast injury in the military environment remains an inherent risk. Primary blast injury can be defined as those caused by direct blast energy or pressure, a form of barotraumas. Closed head injuries due to primary blast are most insidious, elusive and difficult to diagnose. In contrast to secondary and tertiary blast injuries, primary blast injuries are generally limited to air-filled organs of the respiratory, gastrointestinal and auditory systems. Secondary blast injuries are those caused by projectiles created and/or propelled by the blast (shrapnel, rubble, building fragment). Tertiary blast injuries are those due to blast wind causing physical translocation and impact with rigid and stationary objects. Most casualties of blasts in a war environment have experienced some mechanical injury (secondary and tertiary) as well as contribution from primary blast. However, it is extremely difficult to confidently identify cases in which only primary blast injury is present. In the Canadian Forces (CF), the incidence of IED occurs most often in mounted soldiers (within a vehicle); where injuries sustained by the occupants are primarily due to impact of the head against each other, or against structures/obstacles when the vehicle overturns. For example, since the Afghanistan mission, injuries due to IED are twice as prevalent in mounted soldiers as dismounted soldiers (103 and 51 respectively). In other words, the possibility of cortical impact injuries is much higher. In order to develop a comprehensive clinical diagnosis for return soldiers that might experience signs and symptoms of possible brain injury due to cortical impact, we conducted a study comparing motor vehicle accident (MVA) victims where cortical impact are prevalent with an age matched control group using carefully selected neuroimaging and electrophysiological procedures with a validated neurocognitive test battery.

2 Methods

2.1 Motor vehicle accident subjects

Twelve subjects (six males, six females) had a medical diagnosis of mild traumatic brain injury (mTBI) due to a motor-vehicle accident (MVA; mean age 33.19, SD = 13.11). Ten of the MVA patients were right-handed, one was left handed, and one was ambidextrous. Years of education for the patients ranged from Secondary 2 (grade 8) to a Master's degree (mean 12.58 years completed, SD = 2.84). All twelve patients had been employed full time before the accident. Seven had not returned to work since the accident (MVA001, MVA003-005, MVA014, MVA015, and MVA022). Four have returned to their occupations: three to school (MVA011-013) and one is starting a slow and progressive return, working 2 half-days a week (MVA021). The Post-Concussion Symptoms (PCS) scores ranged between 20 and 107 (mean 65.58, SD = 27.92). Nine patients had never suffered major accidents in the past. One patient reported a head trauma in the past (MVA015) and two patients (MVA012, MVA004) reported possible head trauma in the past (e.g. from falling off a bicycle as a child), but none of the three had been suffering from any post-concussion symptoms. Six patients reported past hospitalizations, which included hernia (MVA001, MVA002), lymph nodes (MVA022), bacterial infection and tonsils (MVA003), gallbladder and hand injury (MVA004), and giving-birth and tuberligation (MVA021). Six patients had not had previous hospitalizations (MVA005, MVA011-015). Four patients reported not being on any medication (MVA001, MVA011, MVA012, MVA022). Eight patients used medication for pain (four; MVA003-005, MVA015), concentration (two; MVA013, MVA021), depression & anxiolytics (two, MVA003, MVA021), muscle relaxants (MVA021), leukemia & gout (MVA002), contraceptive (MVA013), and menstrual cramps (MVA014). Five patients had never had a consultation with a psychologist or psychiatrist (MVA001, MVA002, MVA004, MVA011, MVA015). Seven patients had consulted with a psychologist or psychiatrist for various reasons, including while being on stress leave (MVA021), for depression (MVA003), seeing the school psychologist (MVA012), for cognitive assessment (MVA013), personal reasons (MVA022), and related to the accident (MVA005, MVA014).

Eight of the participants in the present study who had sustained a MVA had been in the driver position (MVA001, MVA003, MVA005, MVA012, MVA014, MVA015, MVA021, MVA022). One participant had been in the co-driver's seat (MVA013) and two participants had been seated in the back-seat (MVA004, MVA011). The information for one participant is missing (MVA002). Collisions included frontal impact (five subjects; MVA002, MVA005, MVA013, MVA014, and MVA022), posterior impact (four subjects; MVA001, MVA004, MVA015, and MVA021), lateral impact (MVA003), and three impacts that resulted in the car flipping and spinning before coming to a halt (MVA004, MVA011, and MVA012). Three subjects experienced multiple impacts (MVA004, MVA014, and MVA021). Nine participants wore a seat belt (MVA001, MVA003, MVA005, MVA011-015, and MVA022); two participants did not wear a seat belt (MVA004, MVA021). The information for one participant regarding the wearing of the seatbelt is missing (MVA002). Velocity prior to the accident ranged from 0 to 120 kilometers per hour (mean velocity 66.82 km/h, SD = 39.89). No information regarding velocity is available for one participant (MVA002). The airbag had deployed in three cases (MVA013, MVA015, and MVA022). Seven subjects did not have an airbag available and the airbag of one person did not deploy due to the impact being lateral and of low velocity (MVA003). The information of one participant is missing (MVA002). All participants experienced some loss of consciousness at the time of the accident. Four participants did not have a loss of consciousness (MVA001, MVA005, MVA013, and MVA021), six experienced loss of consciousness of several minutes (MVA003, MVA004, MVA011, MVA012, MVA014, and MVA015). One participant had loss of consciousness for several hours at the hospital (due to induced coma; MVA022) and one participant had loss of consciousness for four days (induced coma due to other health related

issues; MVA002). This latter participant was hospitalized for ten days and, together with the participant in whom loss of consciousness was induced, were the only two that suffered a pneumothorax (MVA002, MVA022). Eight participants reported no retrograde amnesia (MVA001, MVA004, MVA005, MVA012-015, and MVA021); four had retrograde amnesia of several hours (MVA011, MVA022) and two participant of up to one day (MVA002, MVA003). Nine subjects reported no anterograde amnesia (MVA001, MVA002, MVA004, MVA005, MVA012-015, and MVA021), three mentioned light anterograde amnesia of up to several hours post accident (MVA003, MVA011, and MVA022). All of the patients showed signs of confusion and/or disorientation at the site of the accident. The information for one participant is missing (MVA002).

Structural and functional magnetic resonance imaging, electroencephalography, as well as neuropsychological assessments were carried out within 38 to 202 days post injury (mean 122.5 days, SD = 56.04). The control subjects were submitted to the identical test battery as the traumatic-brain injury patients.

2.2 Control Subjects

Here we describe eleven age-matched control subjects (mean age: 34.33, SD = 13.38; five male, six female). The control subjects were healthy and right-handed. Their levels of education ranged from the first year of CEGEP (a public post-secondary education collegiate institution exclusive to the province of Quebec) to a Bachelor's degree (mean 14.91 years completed, SD = 1.51). All subjects, but one, were employed full time at the time of testing. The PCS scores ranged between 0 and 18 (mean 6.82, SD = 6.06). All but one control subject reported not having any past accidents MVA017). The control subject who had had an accident in the past (MVA017), reported not suffering from any post-concussion symptoms. Five control subjects had not had previous hospitalizations (MVA006, MVA009, MVA010, MVA016, and MVA020). Six controls had past hospitalizations for arterial fibrillation as a child (MVA007), pneumonia (MVA017), urinary infection (MVA018), appendix (MVA026), a leg fracture (MVA008), and tonsils and fractures (MVA019). The control subjects reported taking medication for blood pressure (MVA008, MVA017), concentration (MVA017), contraception (MVA018), menstrual cramps (MVA016), and cervical ring for menopause (MVA026). Six control subjects reported not taking medication (MVA006, MVA007, MVA009, MVA010, MVA019, and MVA020). Five control subjects indicated never having had a consultation with a psychologist or psychiatrist (MVA007, MVA008, MVA009, MVA016, and MVA019). Six subjects consulted with a psychologist or psychiatrist for personal reasons (five; MVA006, MVA017, MVA018, MVA020, and MVA026) and for couple therapy (MVA010). None of the participants had a history of alcohol/drug abuse or diagnosed learning disabilities. All subjects gave informed consent.

3 Group Results

3.1 Neuropsychological evaluation

Table 1: Demographics of the MVA victims and control participants

Group		Age	Education	Males:Females	Lefthanders : Ambidextrous : Righthanders
Controls	N	11	11	5:6	0:0:12
	Mean	34.3273	14.9091*		
	SD	13.38014	1.51357		
	SEM	4.03426	.45636		
MVA	N	12	12	6:6	1:1:9
	Mean	33.1917	12.5833*		
	SD	13.11234	2.84312		
	SEM	3.78521	.82074		
Total	N	23	23	11:12	1:1:21
	Mean	33.7348	13.6957		
	SD	12.94912	2.54835		
	SEM	2.70008	0.53		

*Controls had significantly higher education than MVAs (U=30.0 p=.025)

Statistical Analyses: All of the following analyses were done using Mann-Whitney U Tests with a p-value equal to .05. When multiple comparisons were run, the p-value was adjusted using a Bonferroni correction.

3.1.1 Beck Depression Inventory (BDI):

Scores for MVAs and controls differed (U=11.36, p=.001); MVAs had higher scores on the BDI than controls did.

Table 2: BDI mean and standard deviation for MVA victims and control participants

Group	Mean (SD)
MVA	20.67 (10.69)
CTL	4.27 (6.20)

3.1.2 Beck Anxiety Inventory (BAI):

Scores for MVAs and controls differed (U=5.06, p=.024); MVAs had higher scores on the BAI than controls did.

Table 3: BAI mean and standard deviation for MVA victims and control participants

Group	Mean (SD)
MVA	15.75 (9.46)
CTL	7.36 (7.07)

3.1.3 Tower of London:

There were no significant differences between MVAs and controls for any of the ToL variables (Total Correct Score [Problems Solved], Total Move Score, Total Initiation Time, Total Execution Time, Total Time [Problem Solving Time], Total Rule Violations, Total Time Violations).

Table 4: ToL mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	CTL Mean (SD)
Total Correct Score (Problems Solved)	99.58 (25.43)	104.80 (13.21)
Total Move Score	97.25 (26.36)	102.00 (11.66)
Total Initiation Time	104.75 (11.53)	112.80 (20.62)
Total Execution Time	88.50 (28.18)	97.60 (9.28)
Total Time (Problem Solving Time)	86.08 (26.77)	93.00 (14.55)
Total Rule Violations	102.36 (8.14)	104.60 (0.97)
Total Time Violations	96.00 (19.18)	92.40 (19.43)

3.1.4 Wisconsin Card Sorting Task:

There were no significant differences between MVAs and controls for any of the WCST variables (Number of categories, number of cards used, time taken, total correct, total errors, number of perseverative errors, number of non-perseverative errors, unique errors) when the p-value was adjusted for multiple comparisons (original p-value=.05, number of multiple comparisons=8, adjusted p-value=.006). Without the adjustment, there was a significant difference between MVAs and controls for the number of non-perseverative errors (U=5.15, p=.023).

Table 5: WCST mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	CTL Mean (SD)
# of categories	5.00 (1.85)	5.55 (1.51)
# of cards it took the subject	96.91 (21.98)	83.90 (16.54)
Time	549.27 (312.96)	478.78 (254.24)

Total correct	27.10 (25.39)	19.50 (32.42)
Total errors	29.90 (25.62)	10.25 (5.12)
# of perseverative errors	17.80 (19.04)	4.50 (4.32)
# of non-perseverative errors	8.90 (4.77)	3.25 (1.71)
Unique errors	3.56 (6.02)	0.50 (1.00)

3.1.5 Trail Making:

There were no significant differences between MVAs and controls for any of the Trail Making variables.

Table 6: Trail Making mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	CTL Mean (SD)
Condition 1 Std Score	10.92 (1.73)	10.00 (1.26)
Condition 1 Errors	0.0 (0.0)	0.0 (0.0)
Condition 2 Std Score	9.75 (2.42)	10.55 (1.44)
Condition 2 Errors	0.0 (0.0)	0.0 (0.0)
Condition 3 Std Score	9.50 (2.54)	10.36 (1.80)
Condition 3 Errors	0.0 (0.0)	0.0 (0.0)
Condition 4 Std Score	10.33 (1.50)	10.73 (2.45)
Condition 4 Errors	0.42 (0.67)	0.20 (0.63)
Condition 5 Std Score	11.08 (3.72)	11.55 (1.13)
Condition 5 Errors	0.08 (0.29)	0.0 (0.0)

3.1.6 Test of Memory Malingering (TOMM):

There were no significant differences between MVAs and controls for Trial 1, 2, or 3.

Table 7: TOMM mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	CTL Mean (SD)
Trial 1	46.33 (3.60)	48.45 (4.48)
Trial 2	49.82 (0.40)	46.33 (3.60)
Trial 3	49.67 (0.65)	47.35 (4.10)

3.1.7 ReyComplex Figure:

There were no significant differences between MVAs and controls for copying, immediate recall, or delayed recall.

Table 8: Rey Complex Figure mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	CTL Mean (SD)
Copy	2.90 (2.08)	4.67 (2.95)
Immediate	7.40 (3.94)	9.56 (3.17)
Delayed	7.50 (4.19)	9.22 (2.68)

3.1.8 Verbal Word Fluency:

1. MVAs and controls differed significantly in their total (semantic + phonemic) performance ($U= 11.69$, $p<.001$). Comparisons on the subtests revealed that MVAs and controls differed significantly in their total semantic ($U=7.68$, $p=.006$) and phonemic ($U=3.89$, $p=.049$) scores. Comparisons on the semantic subtest components revealed that MVAs and controls differ significantly in their total animal ($U=6.02$, $p=.014$) and food/drink ($U=7.31$, $p=.007$) scores. Comparisons on the phonemic subtest components revealed that MVAs and controls differed only on the letter A performance ($U=6.00$, $p=.014$). Note that when the p-value is adjusted for multiple comparisons (original p-value=.05, number of comparisons=8, adjusted $p=.006$), then the group differences for phonemic, animal, food/drink, and letter A performance is no longer significant.

Table 9: Verbal Word Fluency mean and standard deviation for MVA victims and control participants

Variable	MVA Mean (SD)	CTL Mean (SD)
Semantic	40.57 (7.32)	53.26 (5.80)
Animal	20.42 (4.79)	26.09 (2.74)
Food	20.14 (3.18)	26.81 (4.40)
Phonemic	34.42 (13.99)	45.90 (12.62)
S	12.50 (5.64)	17.00 (5.83)

F	12.50 (5.40)	14.73 (3.35)
A	9.67 (3.80)	14.18 (5.06)

3.1.9 Ruff 2&7:

MVAs and controls did not significantly differ in total speed or accuracy. For Letters, MVAs and controls did not differ significantly for detection speed or errors, but did differ significantly for accuracy (U=5.99, p=.014). For Digits, MVAs and controls did not significantly differ for search speed, errors, or accuracy. For the discrepancy analysis, MVAs and controls did not significantly differ for their speed difference scores, accuracy difference scores, or total difference scores. Note that when the p-value is adjusted for multiple comparisons (original p-value=.05, number of comparisons=11, adjusted p-value=.0045), then the group difference for accuracy in the Letters condition is no longer significant.

Table 10: Ruff 2&7 mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	**CTL Mean (SD)**
Letters – Detection Speed	51.58 (10.00)	50.73 (16.35)
Letters – Detection Errors	4.33 (3.50)	1.91 (1.70)
Letters – Detection Accuracy	50.58 (4.89)	60.27 (12.88)
Digits – Detection Speed	47.33 (6.67)	47.18 (12.73)
Digits – Detection Errors	12.00 (10.31)	6.45 (3.50)
Digits – Detection Accuracy	45.92 (12.62)	52.55 (4.30)
Discrepancy – Speed Difference	4.58 (6.62)	4.72 (9.38)
Discrepancy – Accuracy Difference	6.83 (8.43)	2.45 (4.54)
Discrepancy – Total Differences	7.00 (9.75)	7.82 (14.48)
Total Score – Total Speed	51.33 (8.14)	50.54 (14.40)
Total Score – Total Accuracy	48.00 (8.05)	52.81 (2.93)

3.1.10 Stroop:

For Color Naming, MVAs and controls did not significantly differ in terms of uncorrected or self-corrected errors, time to complete the test, or standard score. For Word Reading, MVAs and controls did not significantly differ in terms of uncorrected or self-corrected errors, time to complete the test, or standard score. For Inhibition, MVAs and controls differed significantly in terms of self-corrected errors (U=6.23, p=.014), but did not differ in terms of uncorrected errors, time to complete the test, or standard score. For Inhibition/Switching, MVAs and controls did not significantly differ in terms of uncorrected or self-corrected errors, time to complete the test, or standard score. Note that when the p-value is adjusted for multiple comparisons (original p-value=.05, number of comparisons=16, adjusted p-value=.003), the group differences for Inhibition self-corrected errors disappears.

Table 11: Stroop mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	**CTL Mean (SD)**

Color Naming – Uncorrected Errors	0.00 (0.00)	0.00 (0.00)
Color Naming – Self-corrected Errors	0.33 (0.49)	0.18 (0.40)
Color Naming – Time	29.58 (5.04)	26.55 (3.14)
Color Naming – Std Score	9.42 (2.47)	10.64 (1.43)
Word Reading – Uncorrected Errors	0.00 (0.00)	0.00 (0.00)
Word Reading – Self-corrected Errors	0.00 (0.00)	0.18 (0.40)
Word Reading – Time	21.17 (3.46)	19.45 (3.70)
Word Reading – Std Score	10.67 (2.10)	11.73 (2.24)
Inhibition – Uncorrected Errors	0.75 (1.36)	0.36 (0.67)
Inhibition – Self-corrected Errors	1.67 (1.37)	0.36 (0.67)
Inhibition – Time	55.67 (11.36)	51.18 (9.81)
Inhibition – Std Score	9.25 (2.86)	10.64 (2.54)
Inhibition/Switching – Uncorrected Errors	0.67 (0.78)	0.64 (1.03)
Inhibition/Switching – Self-Corrected Errors	0.67 (0.89)	0.45 (0.93)
Inhibition/Switching – Time	63.75 (17.44)	57.00 (14.76)
Inhibition/Switching – Std Score	8.83 (4.11)	10.82 (3.12)

3.1.11 California Verbal Learning Test:

There were no significant differences between MVAs and controls for any of the California Verbal Learning variables.

Table 12: California Verbal Learning Test mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	**CTL Mean (SD)**
Total for 5 Trials	54.36 (14.46)	60.00 (12.33)
Trial 1 List A	-0.55 (1.56)	0.35 (1.33)
Trial 2 List A	-0.14 (1.29)	0.45 (1.38)
Trial 3 List A	0.23 (1.33)	0.55 (1.17)
Trial 4 List A	0.45 (1.17)	0.55 (1.14)
Trial 5 List A	0.32 (1.29)	0.45 (0.96)

List B	-0.45 (1.08)	0.00 (0.75)
List A Short Free Recall	0.45 (1.27)	0.85 (0.82)
List A Short Cued Recall	0.23 (1.27)	0.65 (0.82)
List A Long Free Recall	0.45 (1.27)	0.85 (0.85)
List A Long Cued Recall	0.14 (1.34)	0.60 (0.94)
List A Recognition Hits	0.09 (0.70)	0.10 (0.32)
List A Recognition False Positives	2.09 (4.13)	0.60 (1.26)
Forced Choice	14.59 (4.67)	16.00 (0.00)

3.1.12 Wechsler Adult Intelligence Scale (WAIS-111):

MVA and controls differed significantly on their full-scale IQ rating (U=10.07, p=.002). MVAs and controls also differed on their Verbal IQ rating (U=11.96, p=.001), but not on their Performance IQ rating. Analyses on the Verbal IQ subtests revealed that MVAs and controls differed significantly on vocabulary (U=14.14, p<.001) and similarities (U=8.60, p=.003). Analyses on the Performance IQ subtests did not reveal any differences between MVAs and controls when the p-value was adjusted for multiple comparisons (original p-value=.05, number of comparisons=11, adjusted p-value=.0045); without a p-value adjustment, MVAs and controls differed significantly in their Digit Symbol Coding performance (U=3.93, p=.047). No other significant differences in performance were found.

Table 13: WAIS-III mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	**CTL Mean (SD)**
Full Scale IQ	104.75 (5.56)	118.82 (9.76)
Verbal IQ	100.58 (6.22)	122.55 (12.68)
Vocabulary Subtest	50.58 (4.75)	65.91 (7.64)
Similarities Subtest	50.33 (5.59)	60.27 (7.02)
Performance IQ	107.50 (8.91)	110.91 (13.45)
Block Design Subtest	56.08 (5.50)	55.45 (8.03)
Matrix Reasoning	53.58 (7.27)	57.81 (8.72)
Digit Span Total	10.20 (3.08)	10.71 (3.30)
Longest Digit Span Backward	88.40 (9.97)	85.10 (10.28)
Longest Digit Span Backward	82.90 (14.46)	69.80 (35.38)
Digit Symbol Coding	8.91 (2.19)	11.18 (2.71)
Symbol Search	10.25 (1.96)	11.81 (2.27)

Symbol Copy	85.00 (5.20)	91.00 (19.79)
Letter-Number Sequencing	10.08 (2.06)	11.27 (2.20)

3.1.13 Wechsler Memory Scale (WMS-III-Abbreviated):

MVAs and controls showed no significant differences in their WMS standard score, nor in their immediate or delayed memory standard scores. In terms of the immediate and delayed memory subtests, there were no differences between groups when the p-value was adjusted for multiple comparisons (original p-value=.05, number of comparisons=16, adjusted p-value=.003). However, without a p-value adjustment, groups differed significantly in their delayed logical memory standard score (U=4.52, p=.034) and in their delayed logical memory Story B raw score (U=4.71, p=.030).

Table 14: WMS-III mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	**CTL Mean (SD)**
Standard Score	107.00 (4.30)	115.78 (14.68)
Immediate Memory	107.50 (4.37)	112.67 (12.29)
IM – Logical Memory 1 Standard	11.08 (3.36)	13.80 (2.70)
IM – LM – Story A	15.08 (4.83)	17.55 (3.17)
IM – LM – Story B – 1st recall	15.91 (12.77)	15.81 (4.11)
IM – LM – Story B – 2nd recall	16.41 (4.01)	19.64 (3.47)
IM – LM – Family Pictures	10.00 (2.32)	11.10 (2.88)
IM – LM – Family Pictures – Scene 1	13.25 (2.49)	14.63 (1.96)
IM – LM – Family Pictures – Scene 2	13.50 (3.87)	14.45 (2.54)
IM – LM – Family Pictures – Scene 3	10.42 (4.24)	11.00 (3.97)
IM – LM – Family Pictures – Scene 4	9.75 (3.57)	9.81 (4.07)
Delayed Memory	105.60 (5.63)	115.00 (11.61)
DM – LM 2 Standard	11.25 (3.07)	14.20 (2.61)
DM – LM 2 Story A	12.83 (5.18)	15.63 (4.22)
DM – LM 2 Story B	14.41 (4.27)	18.27 (3.22)
DM – Family Pictures	9.83 (2.58)	11.20 (2.93)
DM – Family Pictures Scene 1	12.83 (4.02)	14.81 (1.53)
DM – Family Pictures Scene 2	13.67 (3.77)	14.18 (2.63)
DM – Family Pictures Scene 3	10.41 (4.27)	10.27 (4.10)
DM – Family Pictures Scene 4	9.41 (4.69)	9.81 (4.07)

3.1.14 Grooved Pegboard (Note: all control subjects tested were right handed):

All MVAs (right + left + ambidextrous) & all controls (right only): MVAs and controls significantly differed on only the time to complete the Grooved Pegboard task on the first trial with the right hand (U=4.44, p=.034), however when the p-value was adjusted for multiple comparisons, this was no longer significant (original p-value=.05, number of multiple comparisons=6, adjusted p-value=.008).

Table 15: Grooved Pegboard mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	**CTL Mean (SD)**
Right Hand – 1st	64.81 (9.09)	57.26 (6.31)
Right Hand – 2nd	57.50 (7.89)	56.82 (6.72)
Right Hand Mean	60.15 (6.63)	57.05 (6.22)
Left Hand – 1st	67.63 (14.01)	65.18 (8.84)
Left Hand – 2nd	64.10 (10.74)	64.45 (10.44)
Left Hand Mean	64.65 (11.25)	64.82 (9.23)

3.1.15 MVA Left Hander, MVA Right Handers, All Controls (Right Hand Only):

The control group was made up of right handers only. There was one left hander and 1 ambidextrous in the MVA group; when these participants were grouped together as Left Handers and compared with the MVA right handers and control right handers using an Independent Samples Kruskal-Wallace test, there were no significant differences between groups.

Table 16: Handedness-Grooved Pegboard mean and standard deviation for MVA victims and control participants

	MVA Right Mean (SD)	MVA Left Mean (SD)	CTL Mean (SD)
Right Hand – 1st	61.28 (9.44)	63.50 (12.02)	57.80 (5.16)
Right Hand – 2nd	55.62 (8.10)	59.50 (0.71)	58.00 (4.00)
Right Hand Mean	57.57 (7.12)	61.50 (6.36)	57.80 (3.58)
Left Hand – 1st	67.78 (13.01)	63.50 (7.78)	62.40 (9.34)
Left Hand – 2nd	64.46 (10.28)	59.50 (6.36)	65.60 (13.83)
Left Hand Mean	65.23 (10.65)	61.25 (7.42)	64.00 (11.48)

3.1.16 All MVAs (right + left + ambidextrous) & all controls (right only):

There were no significant differences between MVAs and controls for any of the tapping variables (Right hand first trial, right hand second trial, right hand average, left hand first trial, left hand second trial, left hand average, rapid tapping right hand, rapid tapping left hand, bimanual balanced first trial, bimanual balanced second trial, bimanual balanced average.

Table 17: Tapping mean and standard deviation for MVA victims and control participants

	MVA Mean (SD)	CTL Mean (SD)
Right Hand – 1st	117.00 (30.21)	124.57 (25.21)
Right Hand – 2nd	113.87 (30.62)	128.85 (21.62)
Left Hand – 1st	100.50 (23.99)	117.28 (26.63)
Left Hand – 2nd	105.38 (26.25)	115.57 (21.29)
Bimanual – 1st	25.50 (10.37)	28.85 (11.23)
Bimanual – 2nd	30.88 (17.07)	32.57 (11.65)
Right Hand Mean	114.43 (29.80)	125.57 (23.51)
Left Hand Mean	102.63 (24.84)	116.21 (23.05)
Bimanual Mean	28.06 (13.48)	30.28 (11.38)
Single Tapping – Right	97.00 (13.80)	104.85 (7.66)
Single Tapping – Left	82.87 (33.73)	102.14 (17.57)

Tapping (Note: all control subjects tested were right handed):

3.1.17 MVA Left Handers, MVA Right Handers, All Controls (Right Hand Only):

When the MVA left hander was separated from the right handers and placed in its own group, an Independent Samples Kruskall-Wallace test revealed no significant differences in performance between the MVA left hander, MVA right handers, and control right handers. (Note: the data for the MVA ambixtrous subject was missing for this analysis)

Table 18: Handedness-Tapping mean and standard deviation for MVA victims and control participants

	MVA Right Mean (SD)	MVA Left Mean (SD)	CTL Mean (SD)
Right Hand – 1st	119.88 (29.11)	97.00	128.40 (29.61)
Right Hand – 2nd	117.00 (31.09)	107.00	131.20 (25.24)
Left Hand – 1st	101.37 (23.89)	95.00	123.60 (29.82)
Left Hand – 2nd	105.25 (26.25)	107.00	120.00 (24.36)
Bimanual – 1st	23.75 (5.84)	50.00	29.80 (11.84)
Bimanual – 2nd	27.25 (8.01)	71.00	33.40 (11.59)
Right Hand Mean	117.50 (29.53)	101.50	129.20 (26.95)
Left Hand Mean	103.07 (24.83)	100.50	121.50 (25.97)
Bimanual Mean	25.44 (6.72)	60.00	31.00 (11.699)
Single Tapping – Right	96.63 (13.93)	94.00	107.20 (5.67)
Single Tapping – Left	76.75 (20.76)	118.00	107.80 (11.94)

3.2 Electroencaphalography/Event-related potentials

Test description: Continuous EEG was recorded during the visual version of the externally ordered working memory task (identical to the one used with fMRI) with a high-density recording system (Geodesic 128-Sensor Net, Electrical Geodesics Inc., Eugene, OH, USA). Stimulus presentation and response recording were done with E-Prime for Netstation (Psychology Software tools Inc, Pittsburgh, PA, USA). Task duration was 49 minutes (7 blocks of 7 minutes). Channels were referenced to Cz during acquisition.

Data analysis: Processing of the EEG data was conducted using BrainVision Analyzer(Brain Products GmbH, Munich, Germany). EEG was referenced to the average reference. Continuous EEG was corrected for EOG artefact and filtered with a 20-Hz low-pass filter. EEG was averaged time-locked to the stimulus with a 100 ms pre-stimulus baseline for each condition. Amplitude and latency of the event-related potential (ERP) components was measured relative to the mean of the pre-stimulus baseline for each condition. The following ERP components were measured: 1) N200: a frontal negative component occurring approximately at 200 ms after stimulus presentation and representing working memory processes; 2) N350: a frontal negative component occurring approximately at 350 ms after stimulus presentation and representing working memory processes; 3) P300: a parietal positive component occurring approximately between 300 and 550 ms after stimulus presentation and representing attentional processes. The N200 and N350

components were measured during the encoding phase (stimuli 1 to 4), and the P300 was measured during the decision process (5th stimulus).

3.2.1 Behavioral:

Figure 1 shows the behavioural results for the visual working memory task in MTBI and control groups. The difference observed between the MTBI and control groups for accuracy and reaction times for both control and working memory tasks was not statistically significant. However, a trend was found for lower accuracy in the MTBI group ($p < 0.1$).

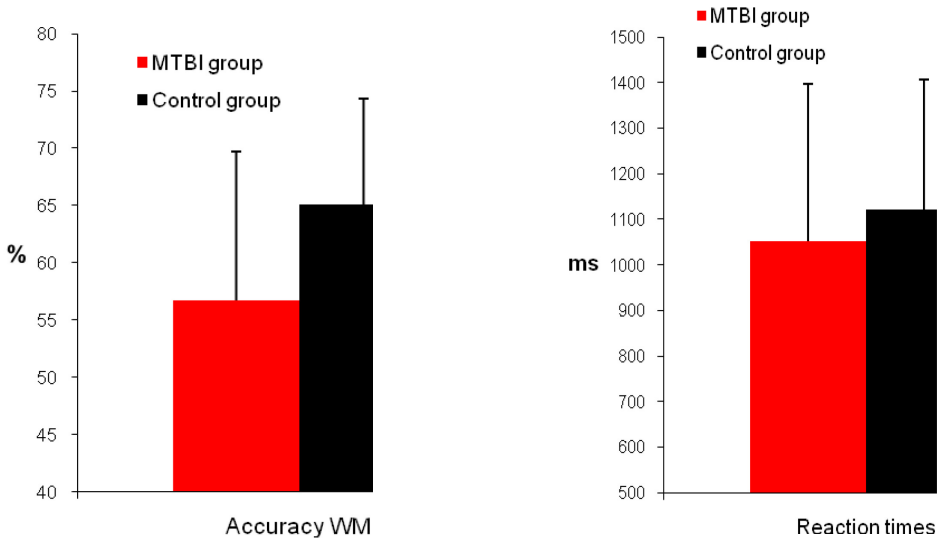


Figure 1: Behavioural results for the visual working memory task in MTBI and control groups.

3.2.2 ERP results, encoding phase - N200:

A clear N200 component can be observed in both groups in Figure 2. No group difference was found for N200 amplitude, latency or scalp distribution:

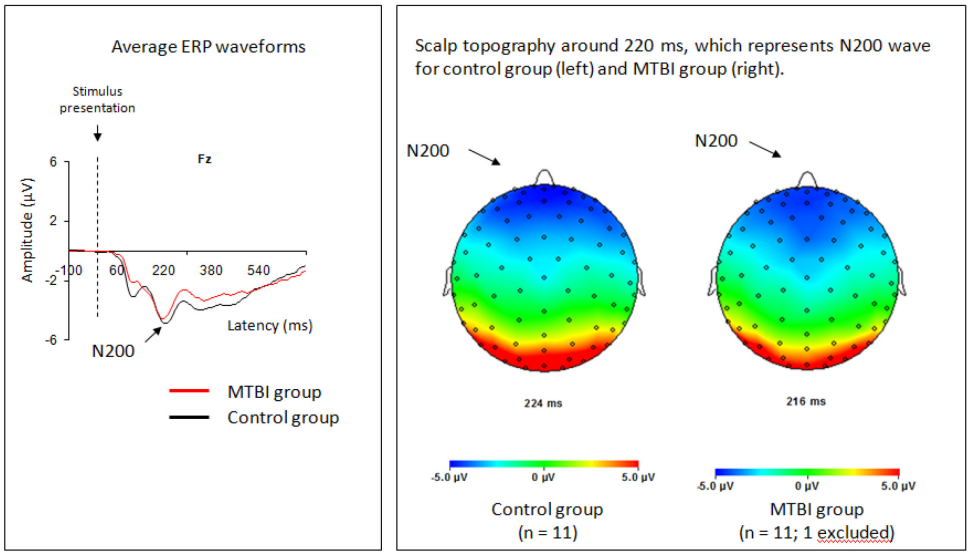


Figure 2 shows the event-related potential (ERP) waveform in the frontal region (left) and the scalp distribution of ERP (right) for the MTBI and healthy control subjects for the encoding phase.

3.2.3 ERP results, encoding phase - N350:

Again, a clear N350 can be observed in both groups, but with smaller amplitude in the MTBI group in comparison with the control group. No group difference was found for N350 latency or scalp distribution.

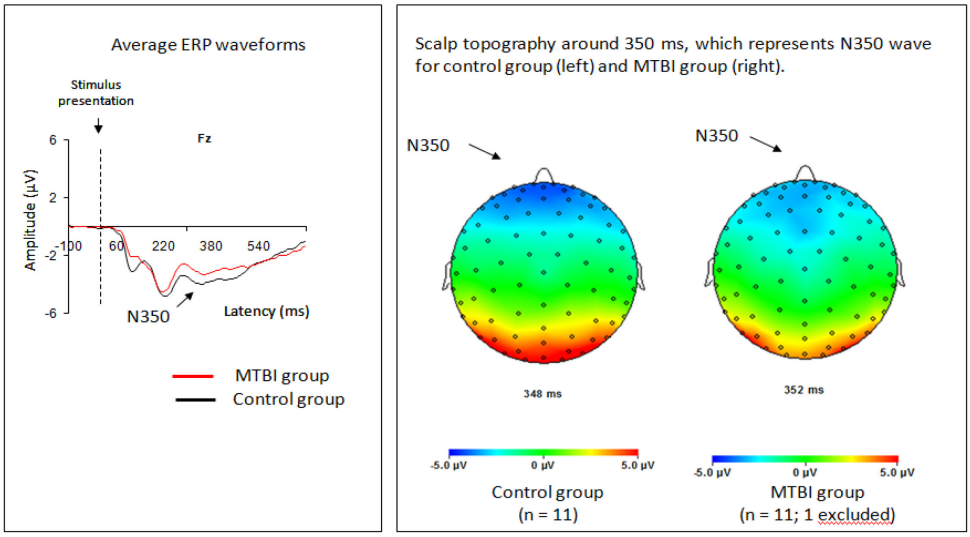


Figure 3 shows the ERP waveform in the frontal region and the scalp distribution of ERP.

3.2.4 ERP results, decision phase - P300:

A clear P300 component can be observed in the posterior region for the control group. A group difference is observed for the amplitude of this component; in fact, MTBI subjects showed a clear reduction in the P300 amplitude in comparison with control subjects. No group difference is observed for latency.

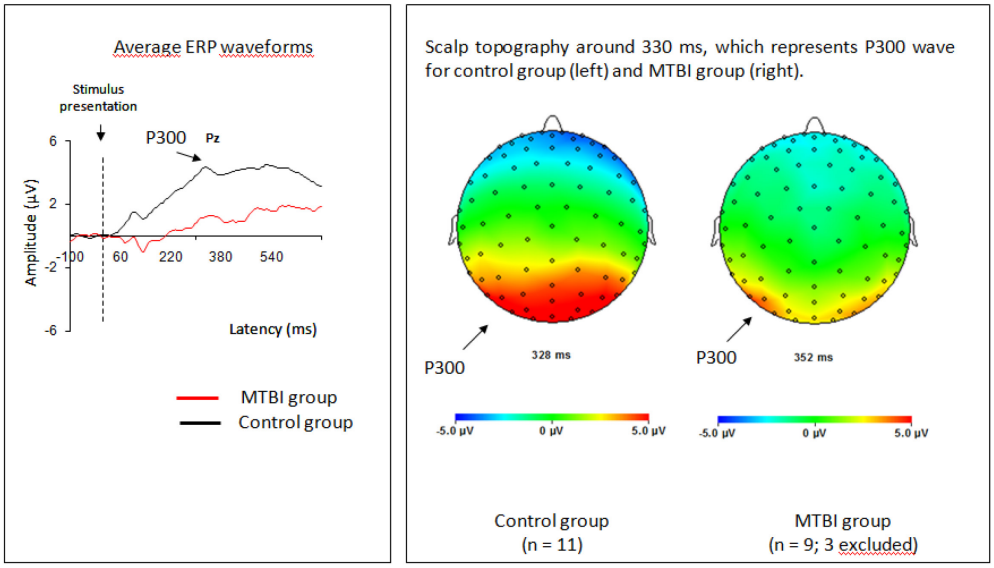


Figure 4 shows the ERP waveform in the parietal region and the scalp distribution of ERP for the decision phase.

3.2.5 Discussion:

No group difference was found for the behavioural results obtained in the visual working memory and control tasks. A clear group difference was observed for the attentional component of the ERP, i.e. the P300. In fact, MTBI subjects had lower P300 amplitudes than control subjects. Amplitude is known to represent the amount of cognitive resources allocated to a task. This reduction in ERP amplitude suggests attentional dysfunctions. However, we have to note that MTBI subjects were able to compensate, at least in part, for this attentional deficit since they obtained normal behavioural results, although there was a trend towards lower accuracy. No group difference was observed for ERP latencies; which are known to represent information processing speed and are in keeping with an absence of group difference in reaction times. Finally, there was a smaller N350 amplitude in the MTBI group while no significant difference was observed for the N200.

3.3 Functional Magnetic Resonance Imaging (fMRI)

We carried out fMRI studies with 11 normal control (NC) and 12 motor vehicle accident (MVA) subjects. Two tasks were used, a working memory task (2 versions, verbal and visual) sensitive to frontal lobe function (i.e. dorsolateral and ventrolateral prefrontal cortices, or DLPFC and VLPFC, respectively), and a navigation task that is sensitive to functioning of medial temporal structures such as the hippocampus and parahippocampus.

Group analyses results Group subtraction analyses of the fMRI data revealed that for the verbal working memory task, the NC group had significantly more activation than the MVA group in several primary regions of interest (ROIs), notably in the left DLPC, bilateral caudate nucleus and

the left thalamus (Figure 5). Control subjects also had significantly stronger activation than the MVA subjects outside the ROI, in the left parietal lobe. For the visual working memory task, the NC group had significantly more activations in bilateral ventrolateral prefrontal cortices and a non-significant trend in the left DLPC ($p = 0.06$) (Figure 6). In addition, the NC group showed significantly more activations than the MVA group in the temporal and parietal lobes bilaterally. For the navigation task, the NC group showed greater activation than the MVA group in the right retrosplenial cortex and a non-significant trend for greater activation in the right hippocampus (Figure 7). These findings are in keeping with our work with symptomatic concussed athletes that also showed reduced brain activations compared to healthy control subjects in key ROIs.

We also measured deactivation in the medial prefrontal region, an area implicated in major depression and shown to be reduced in symptomatic concussed athletes who reported symptoms of depression. Subtraction analysis revealed that the MVA group had reduced deactivation in both rostral anterior cingulate cortex (rACC) and medial orbitofrontal cortex (mOFC) compared to the control group, but the differences were not statistically significant (Figure 8). This result is not unexpected as some of the MVA subjects did not report symptoms of depression, while those with depression were taking medication. Further details can be found in the individual results described below.

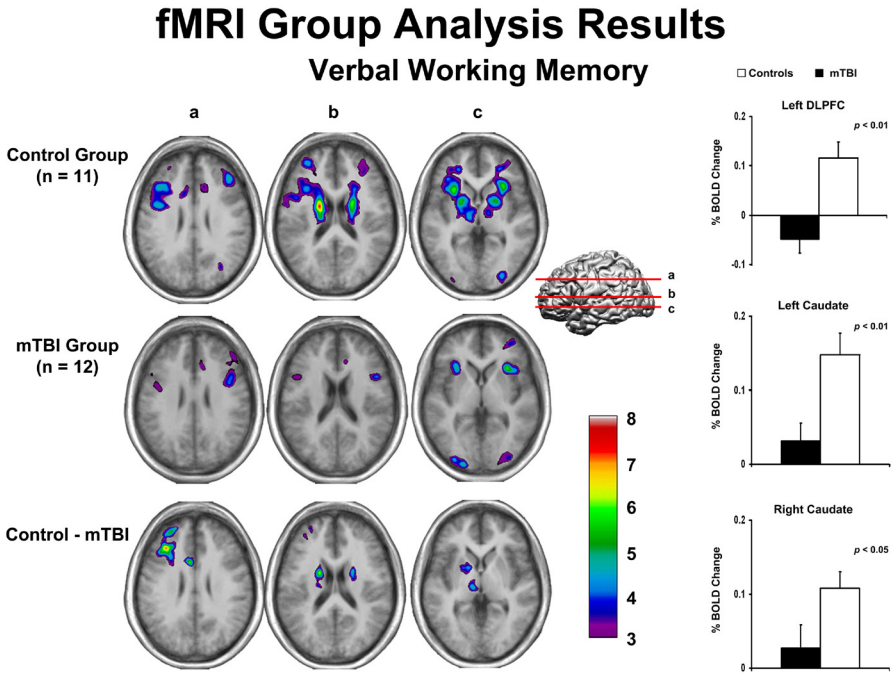


Figure 5 Group analyses for the verbal working memory task for MVA and NC (Images a, b, and c show the BOLD signal within the horizontal plane)

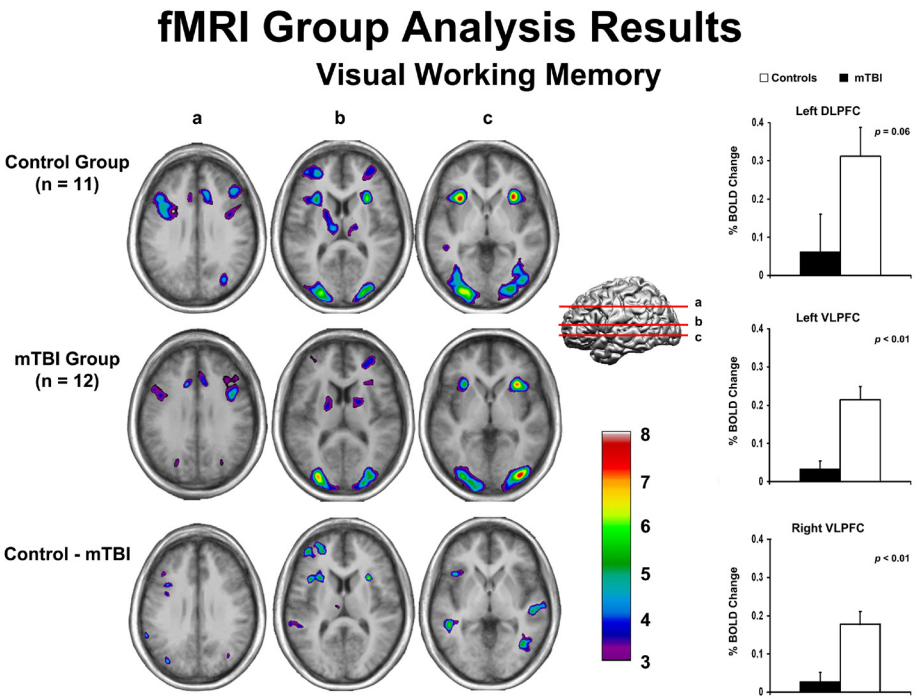


Figure 6. Group analyses for the visual working memory task for MVA and NC (Images a, b, and c show the BOLD signal within the horizontal plane

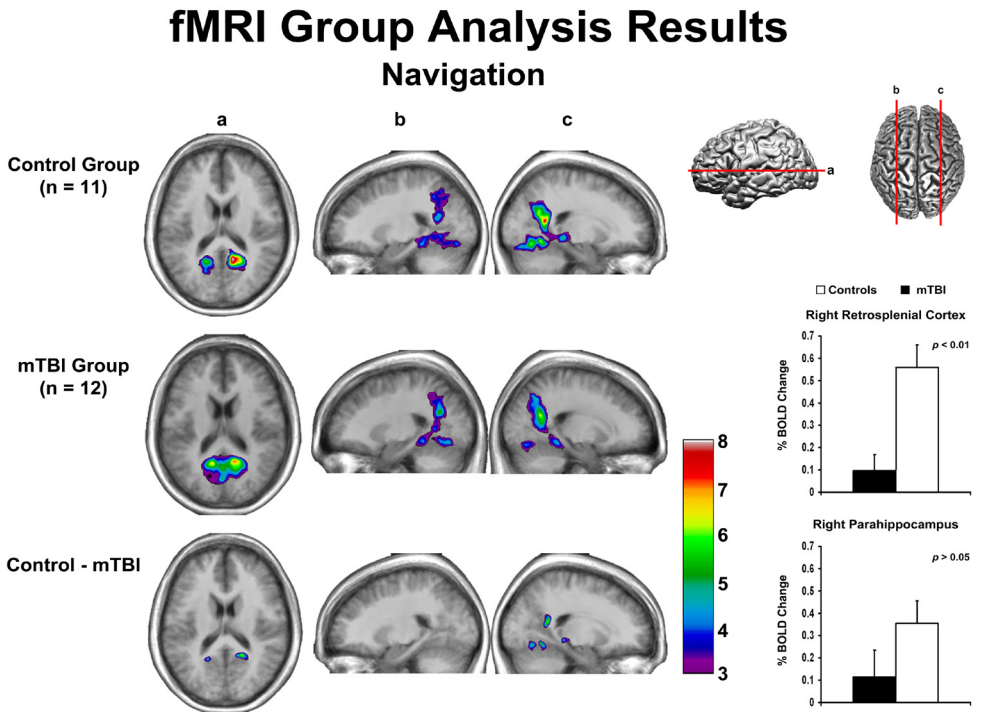


Figure 7. Group analyses for the navigation task for MVA and NC (Image a shows the BOLD signal within the horizontal plane; images b and c illustrate the sagittal plane of the left and right hemisphere, respectively)

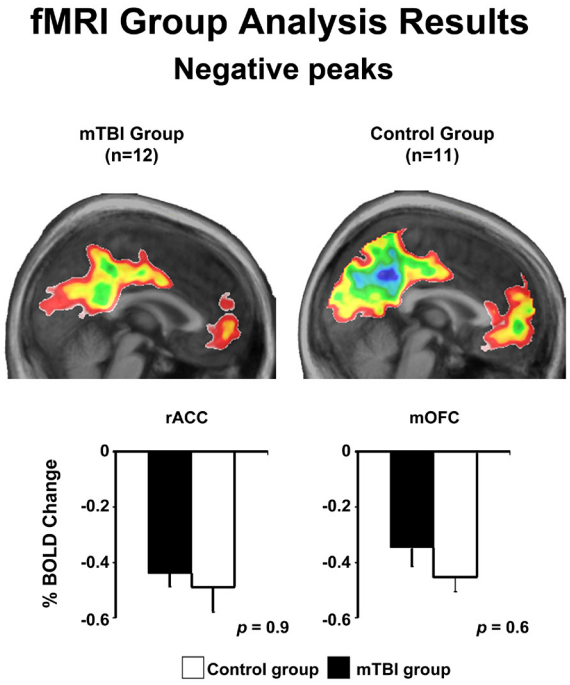


Figure 8. Group analyses results for negative peaks for MVA and NC

4 Individual Results

4.1 Neuropsychological Evaluation

Table 19: Demographics and Intelligence (IQ) Ratings of individual participants

	Age	Gender	Education	Full Scale IQ	Verbal IQ	Performance IQ
MVA001	29	Male	18	95	95	96
MVA002	56	Male	9	114	111	112
MVA003	32	Female	14	106	101	108
MVA004	49	Male	12	102	97	106
MVA005	35	Male	11	103	95*	109
MVA006 (NC)	37	Male	16	118	103*	132
MVA007 (NC)	30	Male	14	122	123	115
MVA008 (NC)	50	Male	16	108	106	108
MVA009 (NC)	54	Male	16	125	133	110*
MVA010 (NC)	34	Female	15	113	106	119
MVA011	21	Female	15	107	109	103
MVA012	20	Male	14	110	96*	126
MVA013	19	Female	11	105	95*	116
MVA014	22	Female	13	109	108	109
MVA015	37	Female	12	95	99	91
MVA016 (NC)	20	Female	16	132	135	120
MVA017 (NC)	20	Male	13	130	140	114*
MVA018 (NC)	21	Female	15	114	116	108
MVA019 (NC)	19	Female	13	122	131	108*
MVA020 (NC)	37	Female	17	124	130	111*
MVA021	50	Female	16	106	106	105
MVA022	24	Male	8	105	95*	109
MVA026 (NC)	52	Female	16	99	94	77

NC = normal control; * significantly lower Verbal or Performance IQ

Table 20: Post Concussion, Depression & Anxiety Scales of individual participants

	Post Concussion	Beck Depression	Beck Anxiety
MVA001	62***	26**	14*
MVA002	20*	5	3
MVA003	102***	39***	35***
MVA004	77***	32***	22**
MVA005	100***	25**	18**
MVA006 (NC)	0	0	5
MVA007 (NC)	2	0	3
MVA008 (NC)	8	3	0
MVA009 (NC)	0	7	4
MVA010 (NC)	5	6	10
MVA011	57***	29**	12
MVA012	24*	3	3
MVA013	65***	24**	21*
MVA014	107***	42***	28**
MVA015	67***	18*	5
MVA016 (NC)	5	0	4
MVA017 (NC)	8	0	4
MVA018 (NC)	15	20*	26*
MVA019 (NC)	12	3	11
MVA020 (NC)	2	0	2
MVA021	55***	19*	16*
MVA022	51***	12	12
MVA026 (NC)	18	3	9

No indication = normal; *= Mild; ** = Moderate; *** = Severe

Table 21: Verbal Memory (T-Scores) of individual participants

	List Learning Total 5 Trials	Delayed	Prose Passages Immediate	Delayed
MVA001	70	63	60	53
MVA002	62	60	60	67
MVA003	73	60	57	63
MVA004	22**	25**	23**	23**
MVA005	60	60	60	57
MVA006 (NC)	72	65	53	57
MVA007 (NC)	36*	40*	53	57
MVA008 (NC)	72	65	64	67
MVA009 (NC)	50	50	60	57
MVA010 (NC)	73	65	57	63
MVA011	51	50	47	50
MVA012	65	65	63	63
MVA013	60	65	60	57
MVA014	59	45	60	53
MVA015	34*	30**	53	50
MVA016 (NC)	54	55	74	74
MVA017 (NC)	53	60	57	60
MVA018 (NC)	70	65	74	74
MVA019 (NC)	55	55	53	50
MVA020 (NC)	65	65	74	74
MVA021	58	65	55	64
MVA022	54	60	43	43
MVA026 (NC)	54	55	53	53

No indication = normal; *= Mild; ** = Moderate; *** = Severe

Table 22: Rey Complex Figure & Family Scenes (WMS-III) of individual participants

	Rey Figure Copy	Rey Figure Immediate Recall	Rey Figure Delayed Recall	Family Pictures Immediate T-Scores	Family Pictures Delayed T-Scores
MVA001	24*	20	13*	40	43
MVA002	31	14*	15*	47	40
MVA003	22*	13*	15*	53	53
MVA004	29	19	22	37***	30***
MVA005	30	24	25	43	43
MVA006 (NC)	31	26	25	50	43
MVA007 (NC)	33	23	23	43	47
MVA008 (NC)	24*	20	20	60	64
MVA009 (NC)	26	13*	15*	37***	40
MVA010 (NC)	29	16*	18	50	50
MVA011	31	27	27	60	57
MVA012	33	29	28	50	53
MVA013	28	22	24	61	61
MVA014	25	11**	6**	57	53
MVA015	18***	12**	14*	53	53
MVA016 (NC)	33	26	28	57	53
MVA017 (NC)	30	20	18	71	71
MVA018 (NC)	35	31	29	60	60
MVA019 (NC)	32	24	22	60	64
MVA020 (NC)	32	17*	15*	50	50
MVA021	31	26	24	50	55
MVA022	31	28	26	50	50
MVA026 (NC)	31	17*	17*	53	53

No indication = normal; *= Mild; ** = Moderate; *** = Severe

Taylor Scoring 36 max.; 18/36 = cutoff for immediate and delayed recall

Table 23: Problem Solving, Executive Function & Verbal Fluency of individual participants

	Stroop Switching T-Scores	Tower Problems Solved	Tower Execution Time T-Score	Wisconsin Card Sorting Categories	Word Fluency T-Scores
MVA001	57	3/10*	37*	3/6**	35*
MVA002	60	5/10	55	6/6	33*
MVA003	37*	4/10*	35*	1/6***	70
MVA004	50	2/10*	38*	2/6**	33*
MVA005	47	6/10	47	6/6	33*
MVA006 (NC)	53	8/10	55	6/6	53
MVA007 (NC)	33*	4/10*	50	6/6	45
MVA008 (NC)	60	1/10*	51	6/6	
MVA009 (NC)	60	6/10	40	6/6	70
MVA010 (NC)	53	8/10	50	6/6	67
MVA011	37*	7/10	50	6/6	37
MVA012	57	8/10	50	6/6	70
MVA013	60	5/10	49	6/6	47
MVA014	40	7/10	51	6/6	47
MVA015	27*	6/10	27***	6/6	37
MVA016 (NC)	60	6/10	50	6/6	37
MVA017 (NC)	60	6/10	53	6/6	63
MVA018 (NC)	40	6/10	50	4/6*	41
MVA019 (NC)	53	5/10	38*	6/10	50
MVA020 (NC)	57	2/10*	45	6/6	53
MVA021	55	3/10*	50	6/6	58
MVA022	23***	6/10	51	6/6	47
MVA026 (NC)	46	5/10	60	1/6***	

No indication = normal; *= Mild; ** = Moderate; *** = Severe

Table 24: Motor Speed and Sequencing of individual participants

	Sequential R	Sequential L	Bimanual
MVA001	Normal	Normal	*
MVA002	*	**	**
MVA003	Normal	Normal	Normal
MVA004	Normal	Normal	**
MVA005	Normal	**	*
MVA006 (NC)	Normal	Normal	Normal
MVA007 (NC)	Normal	Normal	Normal
MVA008 (NC)	Normal	Normal	Normal
MVA009 (NC)	Normal	Normal	*
MVA010 (NC)	Normal	Normal	Normal
MVA011	Normal	Normal	*
MVA012	*	*	Normal
MVA013	Normal	Normal	Normal
MVA014	Normal	*	Normal
MVA015	***	***	***
MVA016 (NC)	Normal	*	Normal
MVA017 (NC)			
MVA018 (NC)	Normal	Normal	Normal
MVA019 (NC)			
MVA020 (NC)			
MVA021	*	Normal	Normal
MVA022	**	**	*
MVA026 (NC)	*	*	*

No indication = normal; *= Mild; ** = Moderate; *** = Severe

4.2 Electroencephalography/Event-related potentials and fMRI

Each MVA subject is compared to an age and sex matched control subject, as well as to the norms established with the data from those twelve matched control subjects, except for subjects MVA022 whose matched control was not yet recruited.

4.2.1 MVA001 vs. NC007:

MVA001 had a PCS score of 62 at the time of the study, which is relatively high. Consistent with his symptom reporting, MVA001's fMRI results showed atypical activation patterns. For the verbal working memory, he did not show significant activation peaks in any of the primary regions of interest (ROI) except in the left thalamus. For visual working memory, a weak activation was found in the left DLPC, a key region for working memory. However, activations were missing in other key brain regions implicated in working memory. As indicated by the histogram in Figure 9, MVA001 had significantly lower BOLD signal change than his matched control in DLPFC for both verbal and visual working memory. Furthermore, the magnitudes of his activations in this region were also below the norm established using the control group data, except in the left DLPFC during the visual task. Finally, compared to the matched control and the normative data, he showed significantly reduced deactivation in the rostral cingulate and medial orbitofrontal cortices (Figure 9). This finding is consistent with the fact that MVA001 was reporting significant symptoms of depression (BDI score = 26). Functional MRI result for the navigation task also showed less than optimal results. MVA001 had significant task-related activations in the retrosplenial cortex. However, he did not show cerebral activation in the left and right parahippocampal gyri, which are known to be important for spatial navigation. This activation pattern is in keeping with his poor performance on the spatial navigation task, in which he was only able to complete 75% of the trials. His neuropsychological profile showed difficulty with the copy and recall of complex visuospatial material as well as poor mental flexibility and planning.

NC007, on the other hand, had very strong activations in all the prefrontal regions of interest, including the dorsolateral and ventrolateral prefrontal cortices. The only atypical finding was in the visual task, where subcortical activation (i.e. caudate nucleus and thalamus) was absent. NC007 showed significant deactivation in the rostral cingulate cortex and medial orbitofrontal cortex, a pattern typically seen in healthy subjects when performing cognitively demanding tasks. Finally, functional MRI results for the navigation task were also in keeping with those of healthy controls, showing significant task-related activations in the retrosplenial cortex, as well as in the parahippocampal gyri.

His neuropsychological profile showed slight sensitivity to interference and weak planning

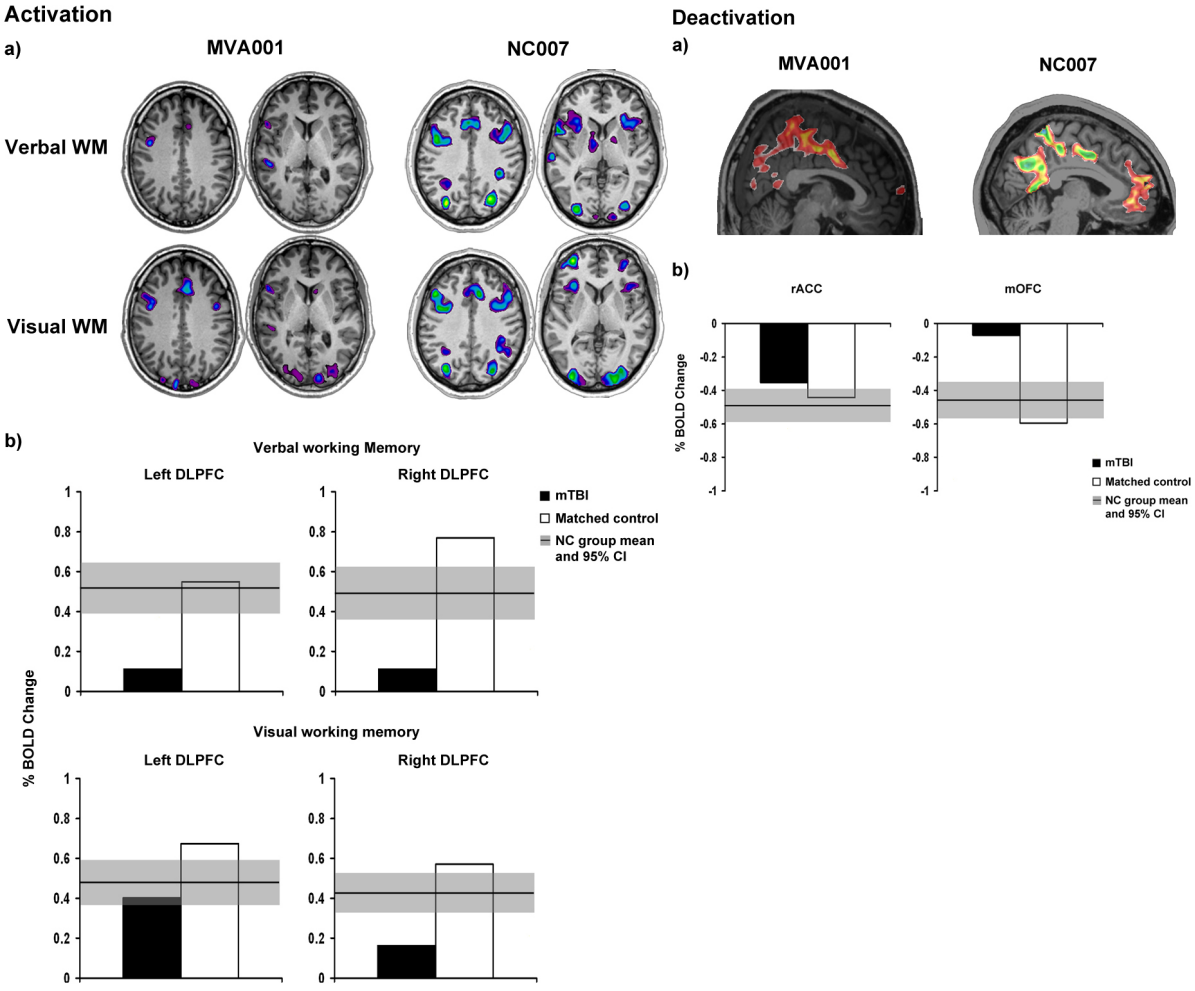


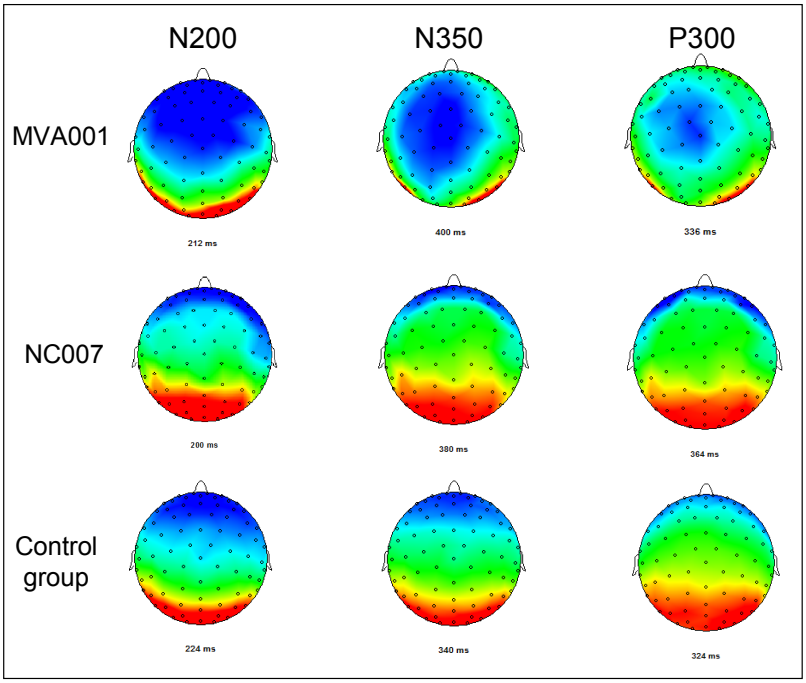
Figure 9: fMRI for MVA 001 vs NC 007

Behavioural data

MVA001
RT: **1706.29 ms**
Accuracy: 71.33%
PCS: 62

NC007
RT: 863.08 ms
Accuracy: 83.33%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA001
Behavioural results: **slower RT** (z score: -2.04,) normal accuracy (z score: -1.25)
N200: normal
N350: normal amplitude, **delayed latency and more posterior distribution**
P300: absent

Figure 10:ERP for MVA001 (MTBO) vs NC007 (control)

4.2.2 MVA002 vs. NC009:

MVA002 had a relatively low PCS score (26) at the time of the study. Consistent with low symptom reporting, MVA002's functional MRI results were encouraging as he showed activations in key brain regions implicated in working memory, except that most of his activation peaks in the primary ROIs were located in the right hemisphere, compared to the bilateral activation pattern seen in controls (**Figure 11)**. For verbal working memory, significant peaks were found in the right DLPFC, bilateral ventrolateral prefrontal cortex, right caudate nucleus and right thalamus. For visual working memory, significant activations were found in the right DLPFC, and bilateral ventrolateral prefrontal cortices. No activation was detected in key subcortical areas, including the caudate nucleus and the thalamus. Quantitative analyses of the ROIs indicate that the magnitude of MVA002's activations were still significantly below the norm, except for the left DLPFC for the visual task. MVA002 did not complain of symptoms of depression, and the pattern of his deactivation was comparable to that of the control (**Figure 11**. For the navigation task, MVA002 had significant task-related activations in the retrosplenial cortex. There was also a strong activation in the right parahippocampal gyrus but not in the left parahippocampal gyrus. This finding is consistent with the mostly right unilateral activations in the main ROIs observed during the working memory task. His neuropsychological profile showed difficulty with the immediate and delayed recall of complex visuospatial material as well weak motor speed and sequencing.

His matched control NC009 showed activation in the prefrontal ROIs, with more robust activation peaks in the left hemisphere. His functional MRI results for the navigation task also

showed the expected pattern of activation in the retrosplenial cortex and the parahippocampal formation. His neuropsychological profile showed difficulty with the recall of visuospatial material as well as slow sequential motor tapping aptitude.

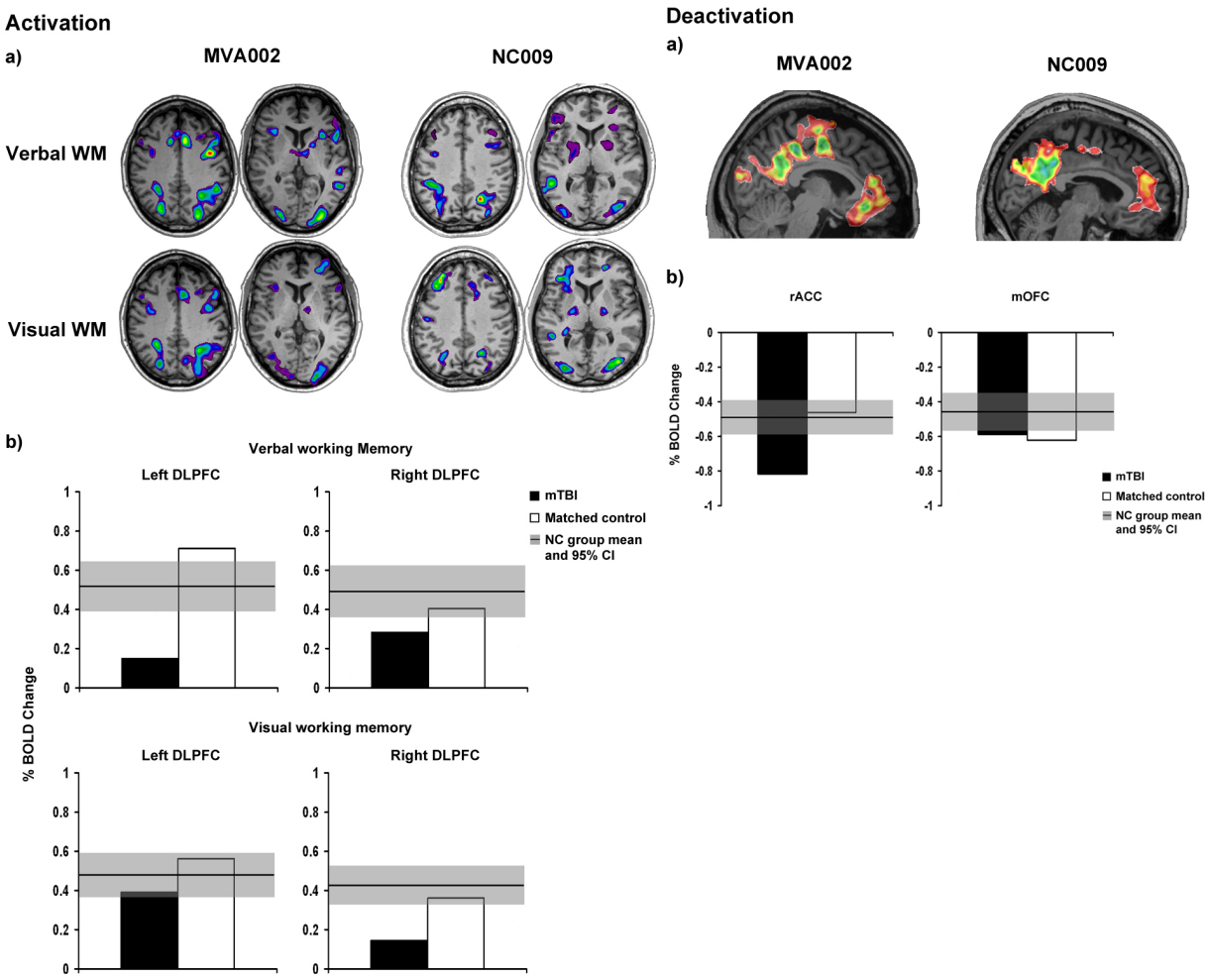


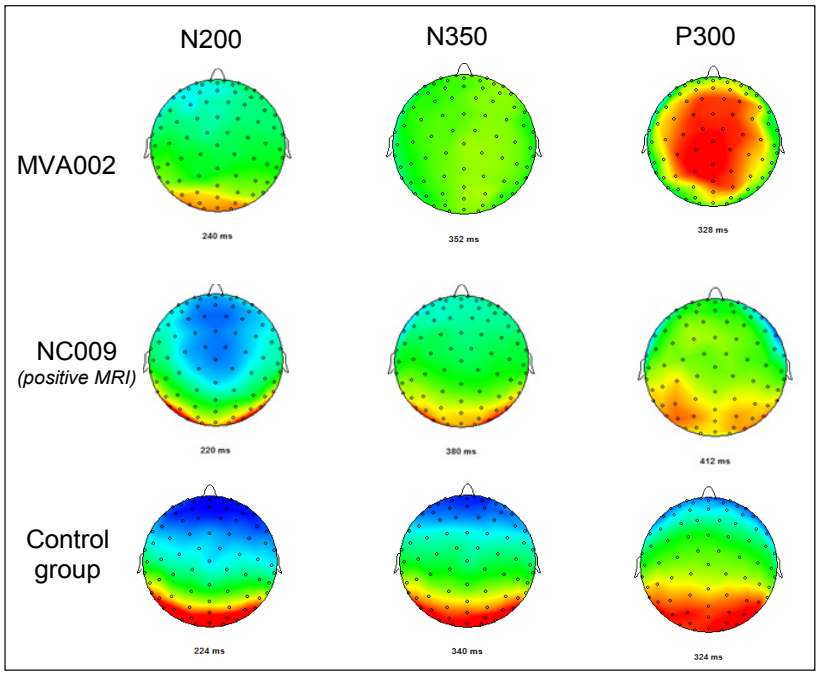
Figure 11: fMRI for MVA 002vs NC 009

Behavioural data

MVA002
RT: 1094.1 ms
Accuracy: 90.0%
PCS: 20

NC009
RT: 1704.4 ms
Accuracy: 87.33%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA002
Behavioural results: normal RT and normal accuracy
N200: small amplitude, normal latency, normal distribution
N350: absent
P300: high amplitude, normal latency, **more anterior distribution**

Figure 12: ERP results : MVA002 vs NC009

4.2.3 MVA003 vs. NC010:

MVA003 had a very high PCS score at the time of the study (102) and did not show significant task-related activation in the ROIs during the verbal working memory task. For visual working memory, weak but nevertheless significant activations were found in the right dorsolateral and ventrolateral prefrontal cortices, both known to be essential for working memory. However, activations were absent in key subcortical areas, including the caudate nucleus and the thalamus. Quantitative analyses revealed that the magnitudes of her activations in the DLPFC were lower than those of the matched control. Furthermore, the magnitude of her BOLD signal change in the right DLPFC was significantly below the norm, while the activation magnitude in the left DLPFC was at the lower end of the normal range (**Figure 13**). In addition to a high PCS score, MVA003 also reported significant symptoms of depression (BDI = 39). The pattern of her deactivation in the medial prefrontal area was comparable to the normative data and that of her matched control (**Figure 13**). This unexpected finding is likely reflecting the effect of the anxiolytic medication she was taking at the time of study. Functional MRI results for the navigation task also showed less than optimal results. MVA003 had significant task-related activations in the retrosplenial cortex. There was also a weak activation in the right parahippocampal gyrus. This activation, however, was sub-threshold and more posterior than that seen in the control group. Furthermore, no activation was found in the left parahippocampal gyrus, a region known to be important for spatial navigation. This finding is corroborated with a poor performance on the spatial navigation task, in which she was only able to complete half of the trials. Her neuropsychological profile showed difficulty with the copy and recall of complex visuospatial material, a high sensitivity to interference as well as poor mental flexibility and planning.

The matched control NC010 showed similar activation pattern to that seen in the other healthy controls, with subtle differences however. For both visual and verbal working memory, significant activations were detected in all prefrontal ROIs, including the dorsolateral and ventrolateral prefrontal cortices. However, activations in the subcortical ROIs (i.e. caudate nucleus and thalamus) were below threshold. The only statistically significant peak was found in the left thalamus during the visual working memory task. Functional MRI results for the navigation task were in keeping with those of healthy controls with significant task-related activations in the retrosplenial cortex, as well as in the parahippocampal gyri. Her neuropsychological profile is essentially normal except for slight difficulty with the immediate recall of a complex geometric figure.

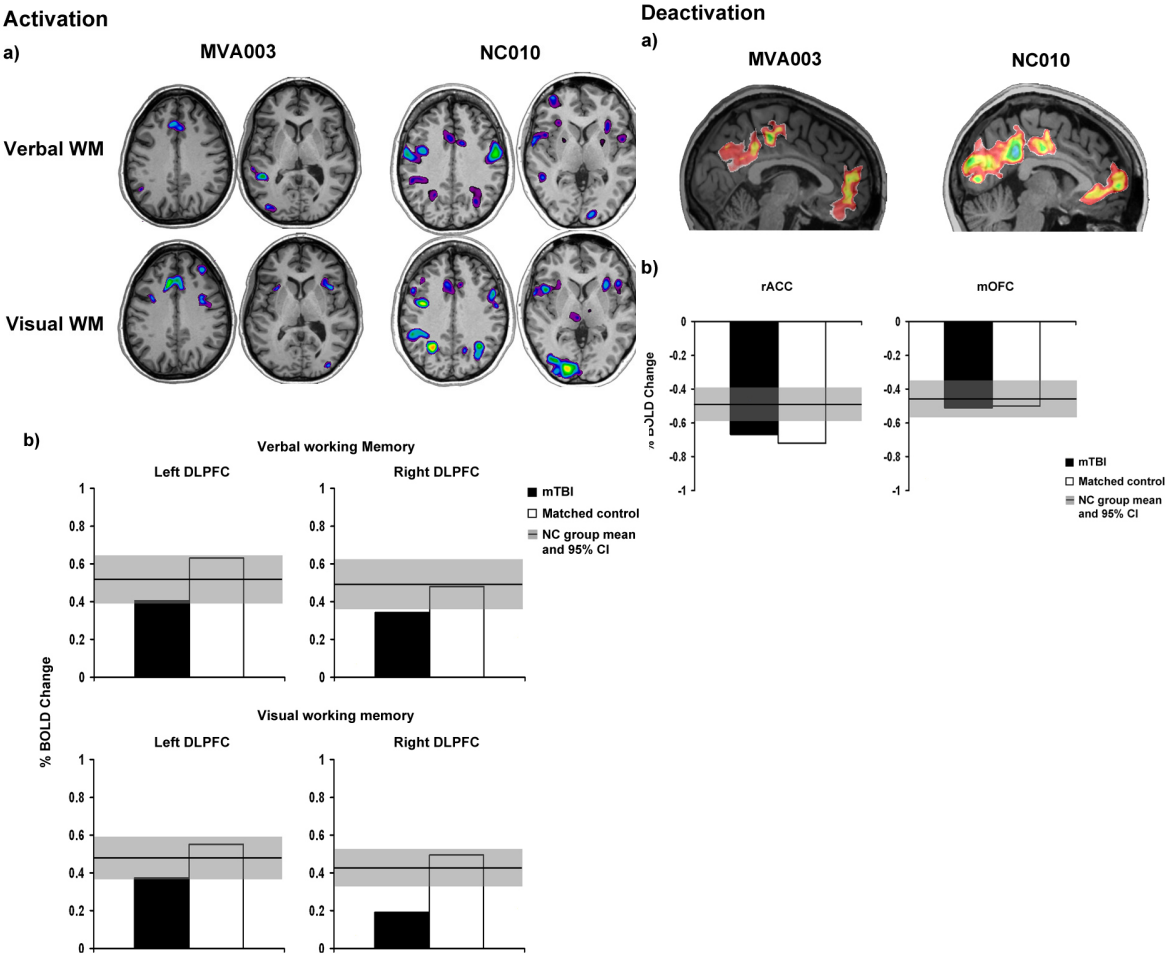


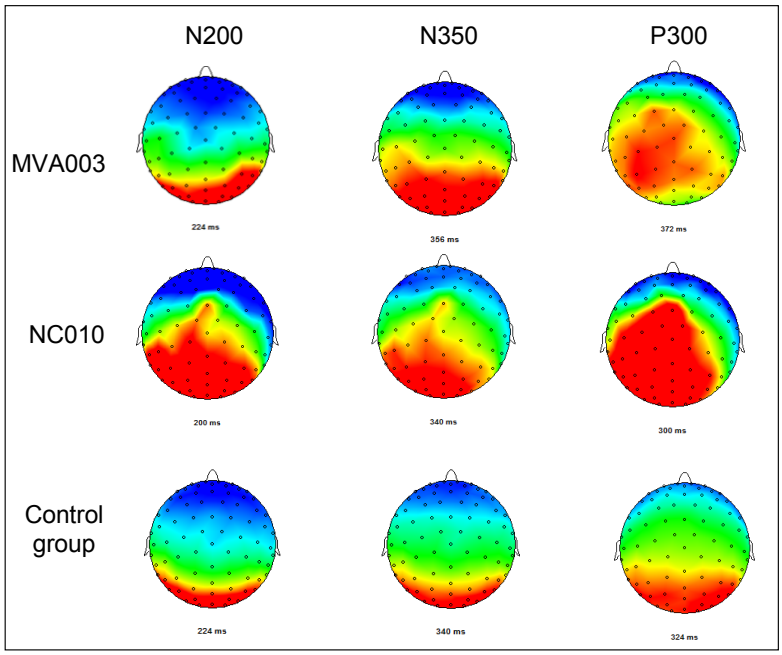
Figure 13: fMRI for MVA 003vs NC 010

Behavioural data

MVA003
RT: 622.3 ms
Accuracy: 89.3%
PCS: 102

NC010
RT: 1043.4 ms
Accuracy: 74.5%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA003
Behavioural results: normal RT normal accuracy
N200: normal amplitude, normal latency, normal distribution
N350: normal amplitude, normal latency, normal distribution
P300: high amplitude, normal latency, **more left hemisphere distribution**

Figure 14: ERP results : MVA003 vs NC010

4.2.4 MVA004 vs. NC008:

MVA004 had a moderate PCS score (77). His fMRI results for verbal working memory showed significant activations in the right dorsolateral and ventrolateral prefrontal cortices. No other activation was found in the primary ROIs, including the left dorsolateral and ventrolateral prefrontal cortex, caudate nucleus and thalamus. Functional MRI results for the visual working memory task were more encouraging as stronger activations were detected in the right dorsolateral and ventrolateral prefrontal cortices. A peak was also detected in the left ventrolateral prefrontal cortex. However, activations were absent in key subcortical areas, including the caudate nucleus and the thalamus. Quantitative analyses indicated that the magnitude of his activations were significantly below the norm in the left DLPFC for the verbal working memory and in the right DLPFC for the visual working memory, a finding consistent with the modalities of the stimuli presented for each task (**Figure 15**). It was also found that the magnitude of BOLD signal changes was within the norm in some of the prefrontal ROIs, which was unexpected given his moderate PCS score. It is noted, however, that MVA004 was taking medication for pain (Naproxen) at the time of the study, and it is unclear whether this drug can have an effect on the activation pattern. This drug may also account for the unexpected deactivation finding, as MVA004 reported significant symptoms of depression although his deactivation pattern was comparable to that of normal controls (**Figure 15**). Functional MRI results for the navigation task also showed less than optimal results. MVA004 had significant task-related activations in the retrosplenial cortex. There was also a weak activation in the right parahippocampal gyrus, but not in the left parahippocampal gyrus. This finding is corroborated with a poor performance on the spatial navigation task, in which he was only able to complete one fifth of the trials. His neuropsychological profile showed difficulty with the learning and recall of verbal and

visuospatial material as well as poor mental flexibility and planning, low word fluency and slow bimanual motor tapping aptitude.

His matched control NC008 showed the typical activation and deactivation patterns expected in a healthy subject. For the verbal working memory, significant peaks were found in the left dorsolateral prefrontal cortex, the left ventrolateral prefrontal cortex and bilateral caudate nucleus. These peaks were lateralized to the left hemisphere compared to the bilateral pattern commonly seen in healthy subjects. This lateralization is, however, consistent with the verbal nature of the task. For visual working memory, significant activations were found bilaterally in the DLPFC, ventrolateral prefrontal cortex, caudate nucleus, and the left thalamus. Functional MRI results for the navigation task also showed the expected activation pattern in the retrosplenial cortex and the parahippocampal formation. His neuropsychological profile was essentially normal.

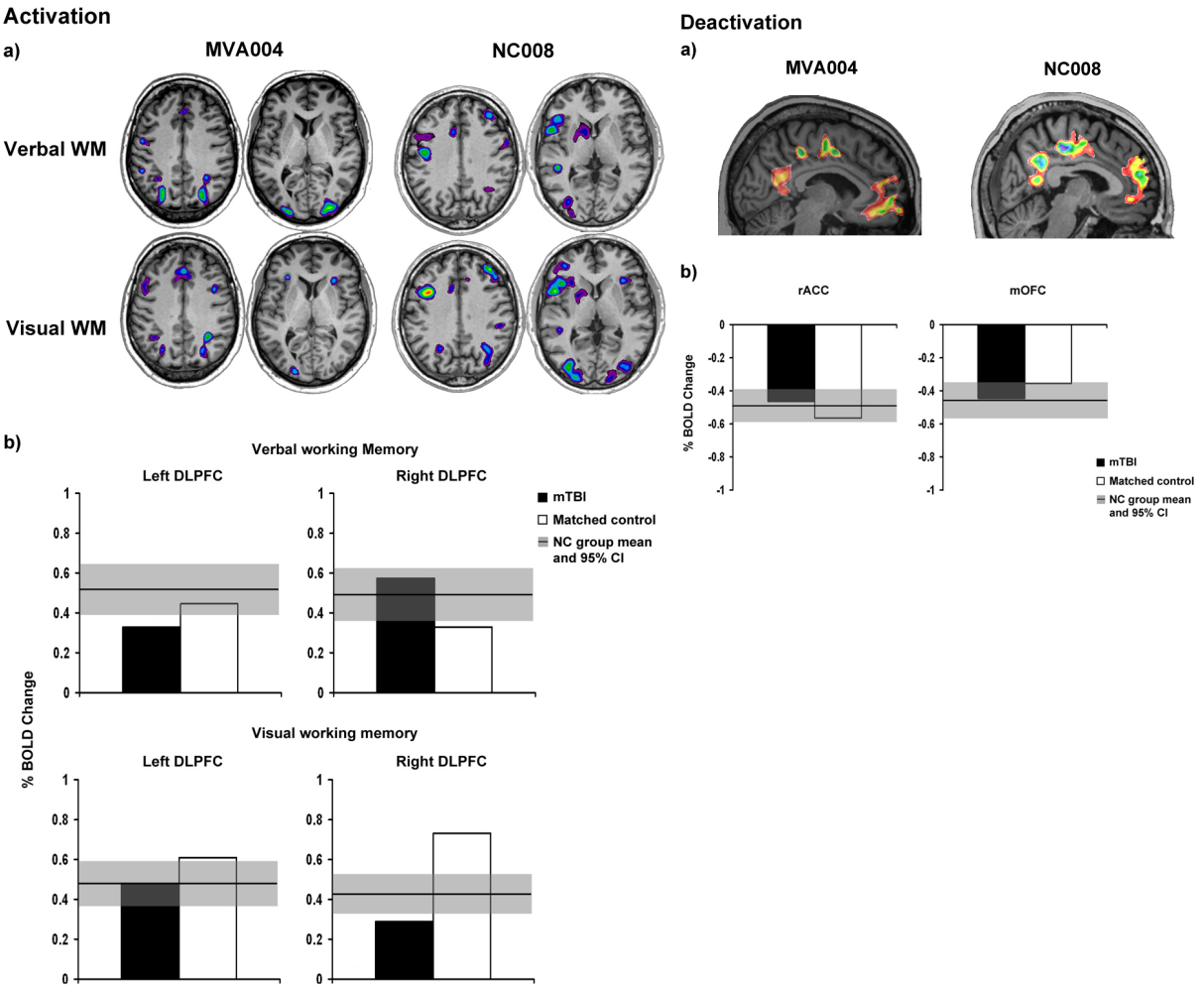


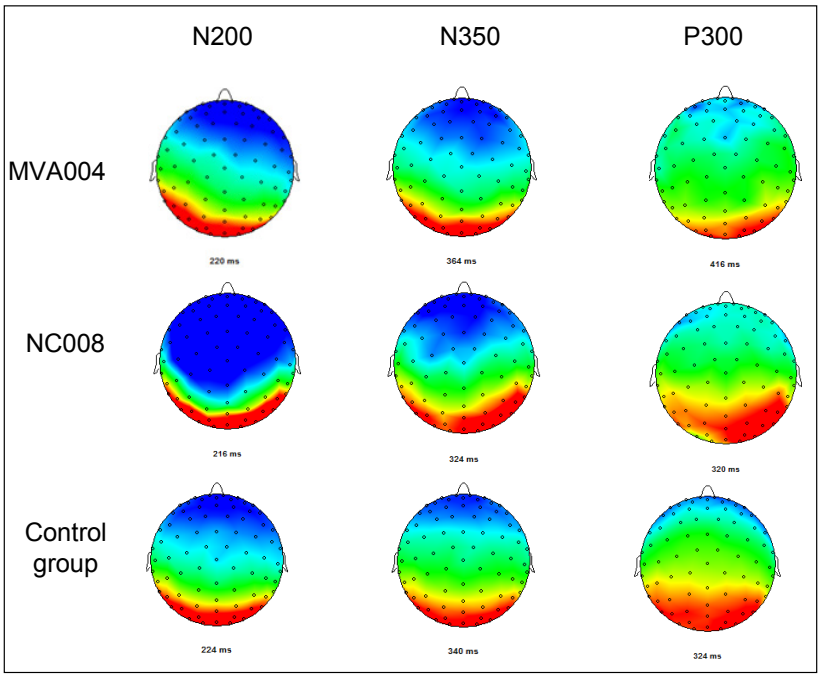
Figure 15: fMRI for MVA 004 vs NC 008

Behavioural data

MVA004
RT: 781,7 ms
Accuracy: **68.7%**
PCS: 77

NC008
RT: 1435.9 ms
Accuracy: 68.5%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA004
Behavioural results: normal RT, **lower accuracy** (z score: -1.5)
N200: normal amplitude, normal latency, normal distribution
N350: normal amplitude, normal latency, normal distribution
P300: small amplitude, delayed latency, very posterior distribution

Figure 16: ERP results : MVA004 vs NC008

4.2.5 MVA005 vs. NC006:

MVA005 had a very high PCS score (100) at the time of study. For verbal working memory, weak activations were detected only in the DLPFC. While the DLPFC is an important cortical region implicated in working memory, there are other critical brain regions in this cognitive process, such as ventral lateral prefrontal cortex, caudate nucleus and thalamus that were not activated. Functional MRI results for visual working memory appeared more typical as significant activations were found in the dorsolateral and ventrolateral prefrontal cortices (i.e. in all prefrontal ROIs). However, quantitative analyses confirmed that the magnitude of the activations was significantly lower than the norm and that of his matched control except in the right DLPFC for the verbal task (**Figure 17**). MVA005 had a depression (BDI) score of 25 but the pattern of his deactivation was comparable to the norm and to the matched control (**Figure 17**). Like MVA004, this subject was also taking medication for pain at the time of the study, which may have had an effect on fMRI activation. For the navigation task, MVA005 had a similar activation pattern as that seen in healthy controls. Significant task-related activations were found in the retrosplenial cortex, as well as in the left and right parahippocampal gyri. This finding is corroborated with a good performance on the spatial navigation task, in which he was able to complete 90% of the trials. His neuropsychological profile showed a low word fluency output and slow sequential tapping with the left hand and both hands simultaneously.

The matched control NC006 had an atypical activation pattern for a healthy subject. For verbal working memory, significant activation was detected in the right DLPFC and the left ventrolateral prefrontal cortex. No activation was found in the subcortical ROIs (i.e. caudate nucleus and

thalamus). Stronger activation patterns for the visual working memory task were detected in all the prefrontal ROIs. But again, no activations were detected in the subcortical regions. Functional MRI results for the navigation task also showed atypical results. Significant task-related activations were found in the retrosplenial cortex, but no activation was detected in the left and right parahippocampal gyri, which are known to be important brain regions for spatial navigation. His neuropsychological profile was normal.

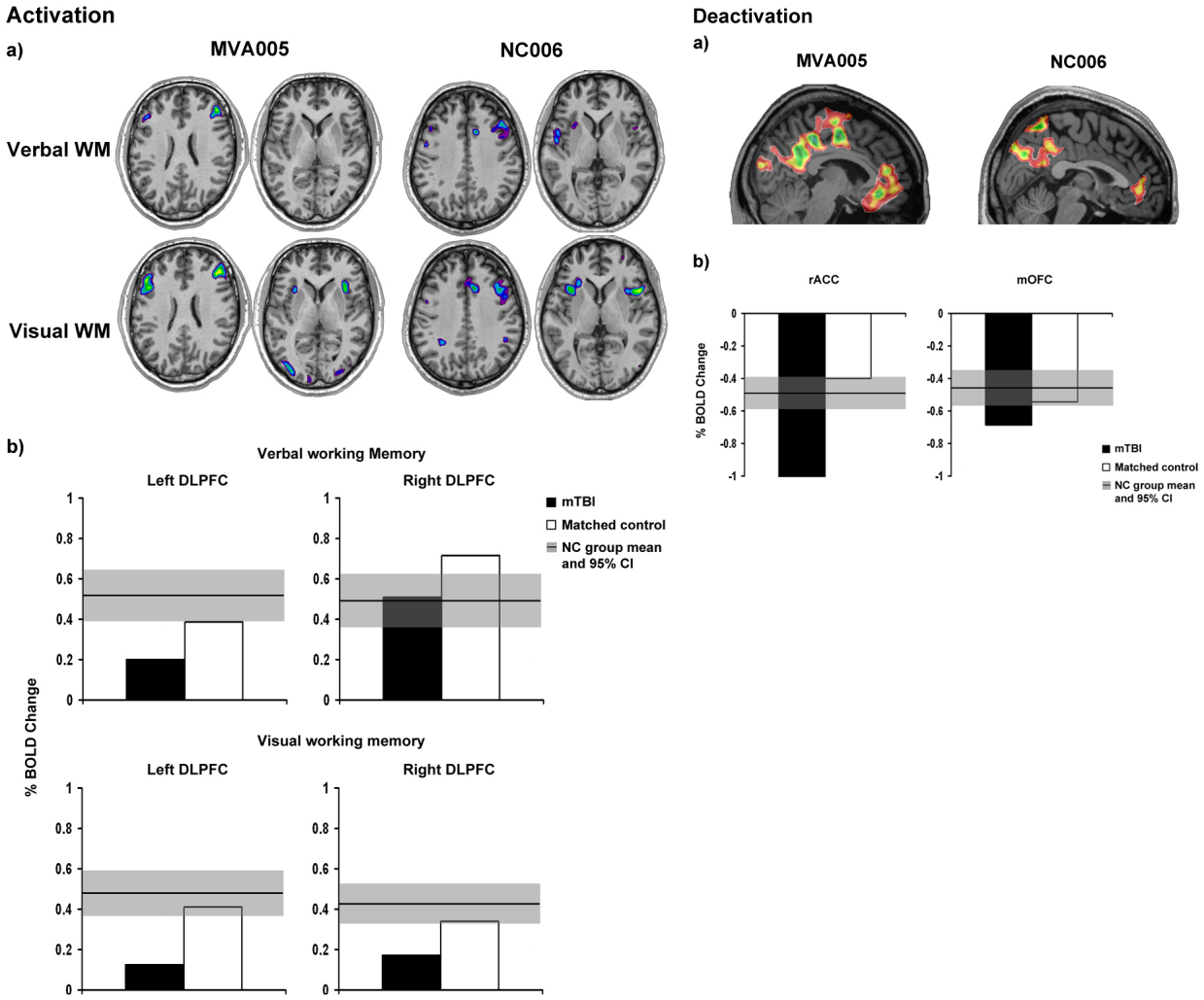


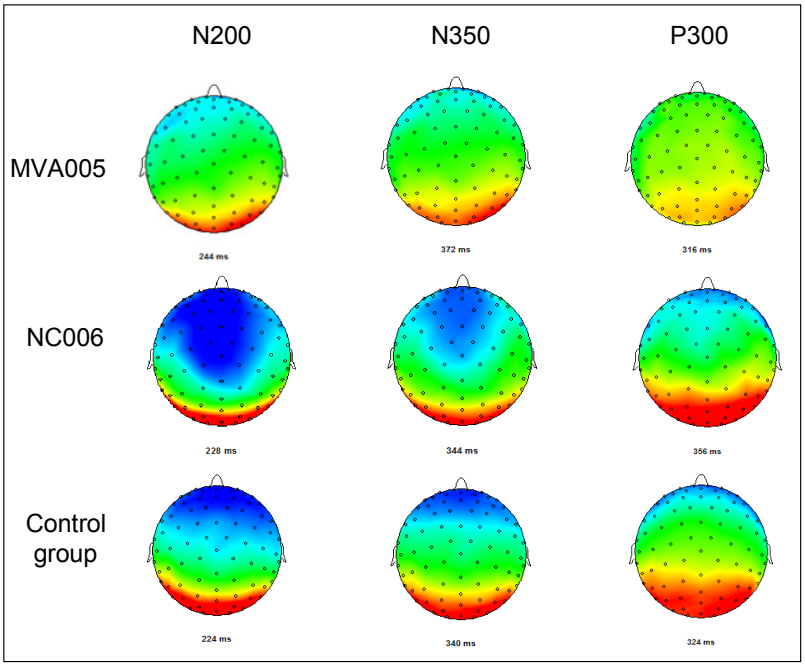
Figure 17: fMRI for MVA 005 vs NC 006

Behavioural data

MVA005
RT:1486.3 ms
Accuracy: 83.3%
PCS: 100

NC006
RT: 883.9 ms
Accuracy: 63%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA005
Behavioural results: normal RT and normal accuracy
N200: small amplitude, delayed latency, normal distribution
N350: small amplitude, delayed latency, normal distribution
P300: small amplitude, delayed latency, normal distribution

Figure 18:ERP results : MVA005 vs NC006

4.2.6 MVA011 vs. NC018:

MVA011 had a moderate PCS score at the time of the study (57), and she showed extreme difficulties on the working memory tasks. Consistent with her symptom reporting and difficulties on the tasks, MVA011's functional MRI showed atypical brain activation patterns. For the verbal working memory, MVA011 did not show any task-related activation in the primary ROIs. For the visual task, the only activation within the primary ROI was found in the right DLPFC. Furthermore, MVA011 did not show significant deactivation in the rostral cingulate cortex and medial orbitofrontal cortex, which is in keeping with her high BDI score (29). Quantitative analyses of the activations and deactivations indicated that the magnitudes of her BOLD signal change were significantly reduced in all ROIs (**Figure 19**). The functional MRI results for the navigation task showed more encouraging results as significant activation peaks were detected in the retrosplenial cortex and the posterior parahippocampal gyri, although the magnitude of activation in the right parahippocampus was relatively weak. Her neuropsychological profile showed a high sensitivity to interference and slow bimanual sequential tapping aptitude.

The matched control NC018 showed activation typically seen in a healthy subject. For verbal working memory, significant peaks were found in all primary ROIs, including bilateral DLPFC, left ventrolateral prefrontal cortex, bilateral caudate nucleus and left thalamus. Compared to the verbal task, the activation pattern for the visual working memory was slightly weaker. Significant activations were found in the right dorsolateral prefrontal cortex and bilateral ventrolateral prefrontal cortex. For the subcortical regions, only sub-threshold activations were detected in the right caudate nucleus and thalamus. Finally his functional MRI result for the navigation task

showed the expected activation pattern in the retrosplenial cortex and the parahippocampal formation. Her neuropsychological profile was normal.

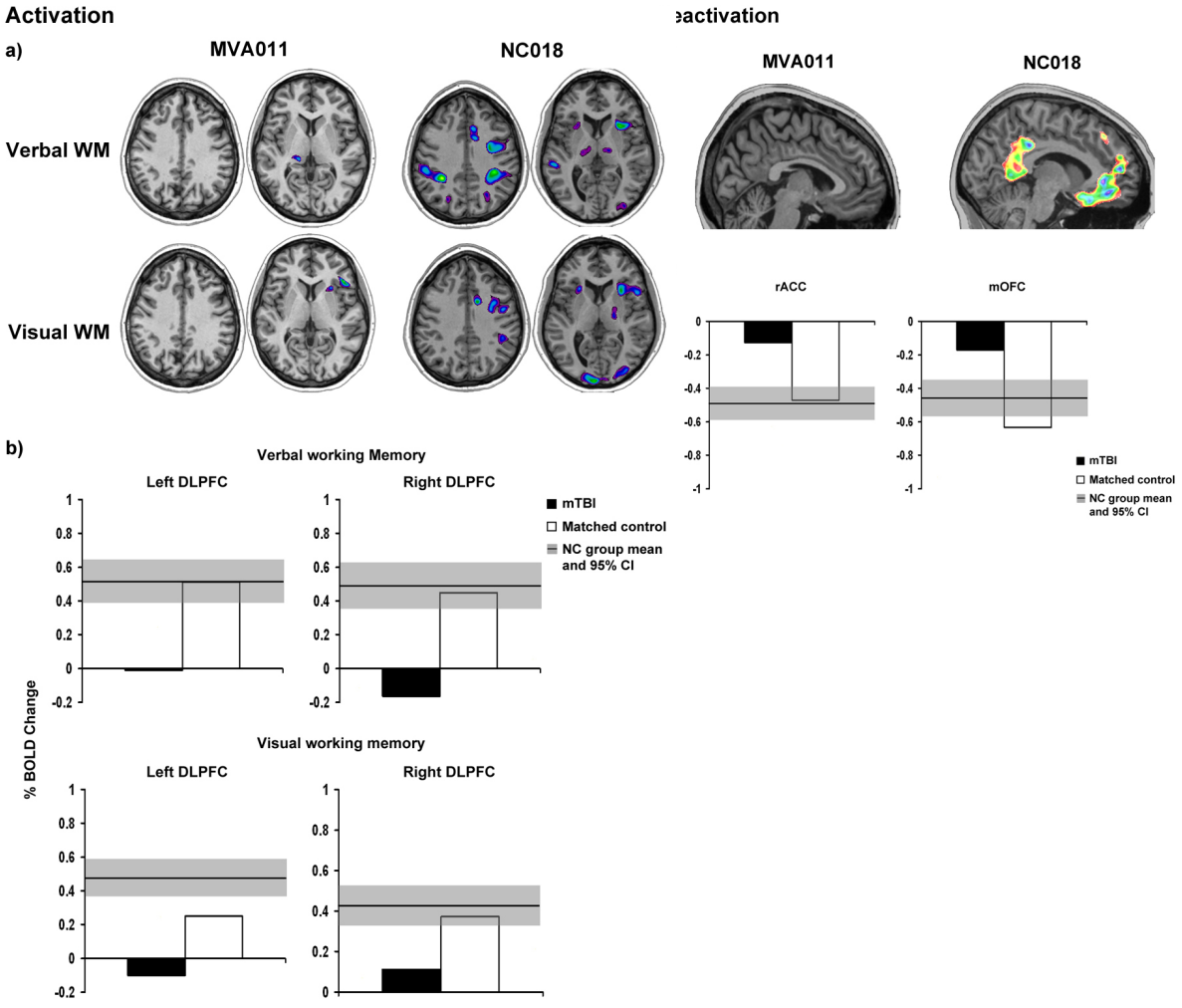


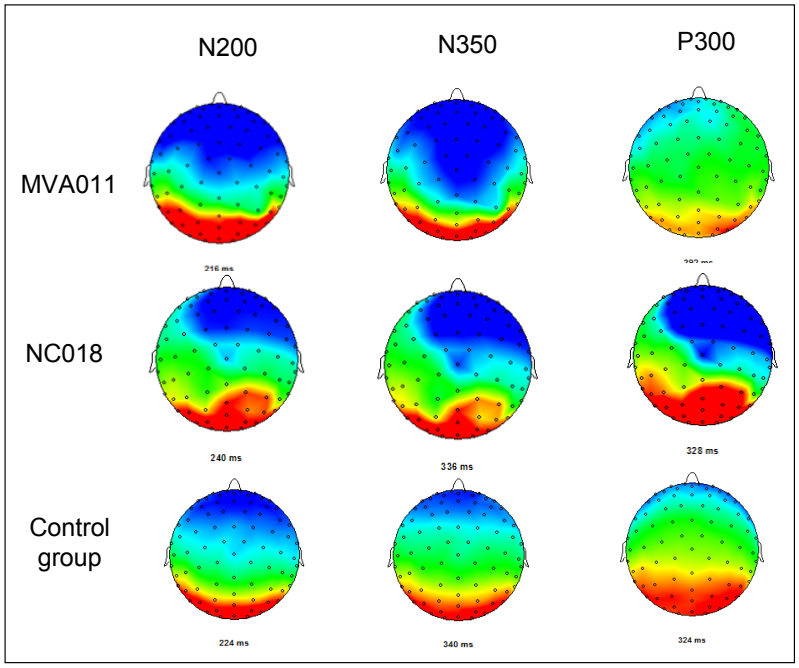
Figure 19: fMRI for MVA 011 vs NC 018

Behavioural data

MVA011
RT:792.1 ms
Accuracy: **54%**
PCS: 57

NC018
RT: 970.6 ms
Accuracy: 78.7%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA011
Behavioural results: normal RT, **lower accuracy** (z score: -2.7)
N200: normal amplitude, normal latency, normal distribution
N350: normal amplitude, normal latency, normal distribution
P300: small amplitude, normal latency, normal distribution

Figure 20: ERP results : MVA011 vs NC018

4.2.7 MVA012 vs. NC017:

MVA012 had relatively mild symptoms at the time of the study (PCS=24). In keeping with low symptom reporting, MVA012's functional MRI activation patterns are, in general, similar to those of normal healthy controls with some minor deviations. For the verbal working memory, significant activations were detected in all prefrontal ROIs. Atypical findings were noted, however, in subcortical regions as MVA012 did not show any significant activation in the caudate nucleus and the thalamus. For the visual task, significant activations were found in all prefrontal and subcortical ROIs. Quantitative analyses indicated that the magnitudes of his activations were all within the normal range except for the right DLPFC during verbal working memory (**Figure 21**). MVA012 was not reporting symptoms of depression and the pattern of deactivation in his medial prefrontal region was normal (**Figure 21**). For the navigation task, MVA012 also showed the typical activation pattern seen in normal healthy subjects, with significant activations in the retrosplenial cortex and the parahippocampal gyri. His neuropsychological profile was essentially normal except for slow unimanual sequential tapping aptitude.

NC017, on the other hand, showed rather weak activations for a healthy control. For the verbal working memory, MVA017 did not have any significant activation in the primary ROIs, except for a weak peak in the left ventrolateral prefrontal cortex. This finding highlights the importance of a solid control database, and the usefulness of group normative data. The results for the visual task were more encouraging as more activations were detected in the primary ROIs, including the left DLPFC, left ventrolateral prefrontal cortex, and bilaterally in the caudate nucleus. Finally the

result for the navigation task showed the expected activation pattern in the retrosplenial cortex and the parahippocampal formation. His neuropsychological profile was normal.

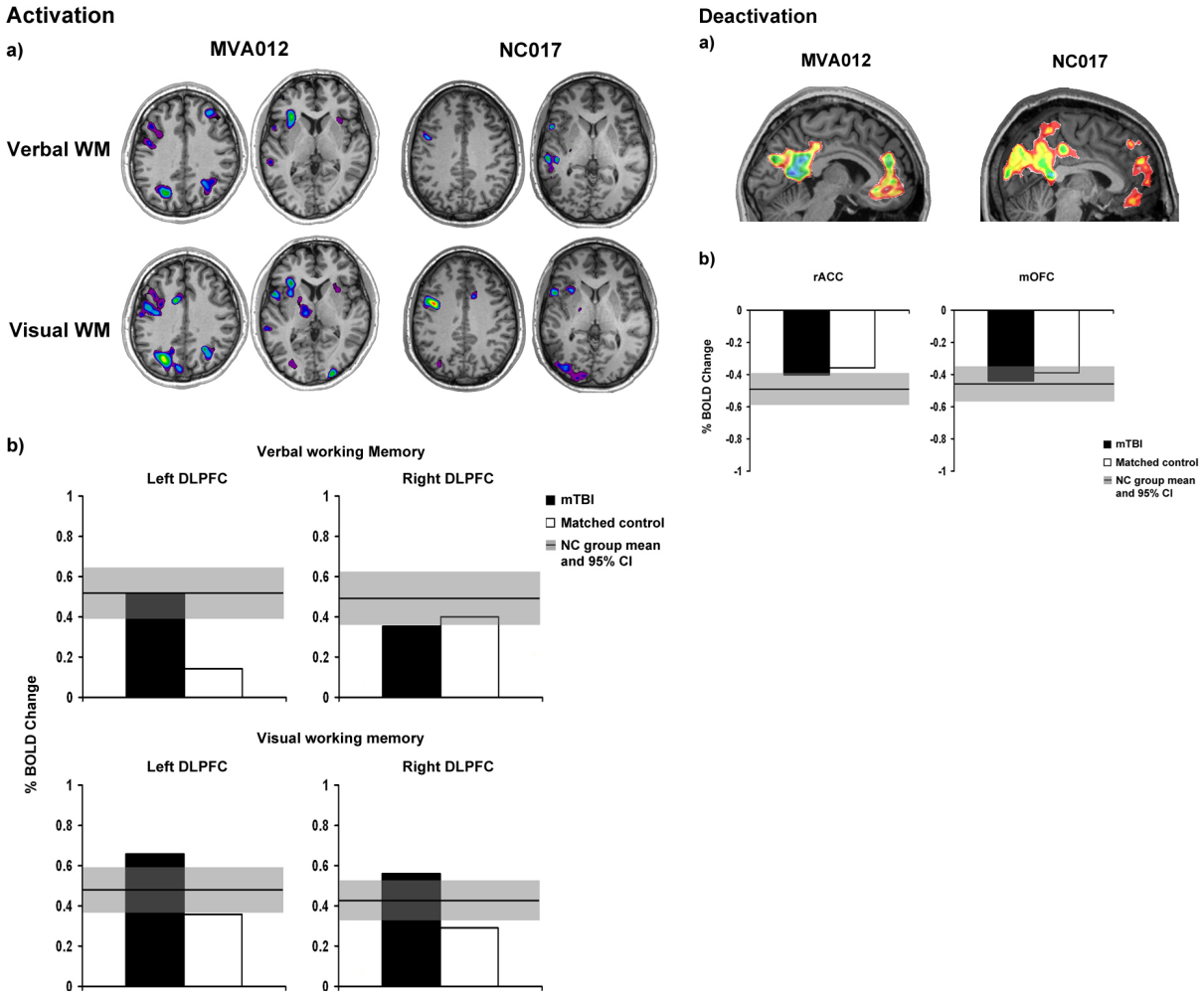


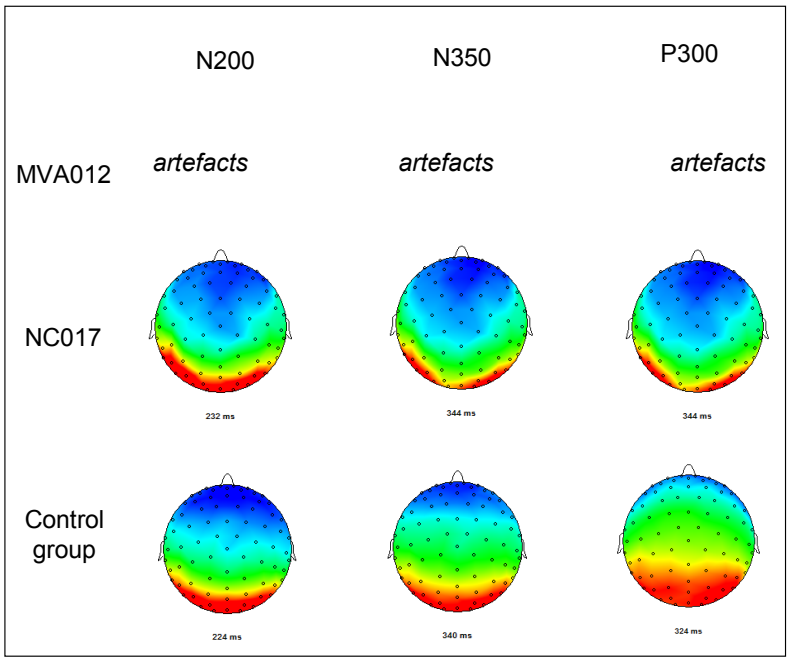
Figure 21: fMRI for MVA 012 vs NC 017

Behavioural data

MVA012
RT: 953.8ms
Accuracy: 94.7%
PCS: 24

NC017
RT: 1275.1 ms
Accuracy: 43%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA012
Behavioural results: normal RT, normal accuracy
N200: na
N350: na
P300: na

Figure 22: ERP results : MVA012 vs NC017

4.2.8 MVA013 vs. NC019:

MVA013 had a moderate PCS score (65) at the time of the study. Consistent with her symptom reporting, her functional MRI showed atypical brain activation patterns. For verbal working memory, activations were detected only in the ventrolateral prefrontal cortex bilaterally. No activation was found in other key ROIs implicated in working memory, such as the DLPFC. For visual working memory, the only significant activation within the primary ROIs was detected in the left thalamus. Quantitative analyses revealed that MVA013 had significantly lower activation magnitude in the DLPFC for both verbal and visual working memory tasks (Figure 23).

Furthermore, MVA013 showed much reduced deactivation in the medial orbitofrontal cortex (Figure 23). This finding is consistent with her high symptom reporting on the Beck Depression Inventory-II (BDI score = 24). The functional MRI result for the navigation task was more encouraging as significant task-related activations were found in the retrosplenial cortex and the posterior parahippocampal gyri. Her neuropsychological profile was essentially normal.

NC019 shows an activation pattern similar to that seen in normal healthy subjects as activation peaks were found in most primary ROIs, except in the subcortical areas (i.e. caudate nucleus and thalamus) where the magnitude of activation was less pronounced. NC019 had significant deactivation in the rostral cingulate cortex but a slightly lower deactivation in the medial orbitofrontal cortex. This finding is in accordance with her slightly elevated score (11) on the Beck Anxiety Inventory. Finally, functional MRI result for the navigation task showed the expected activation pattern in the retrosplenial cortex and the parahippocampal formation. Her neuropsychological profile was normal.

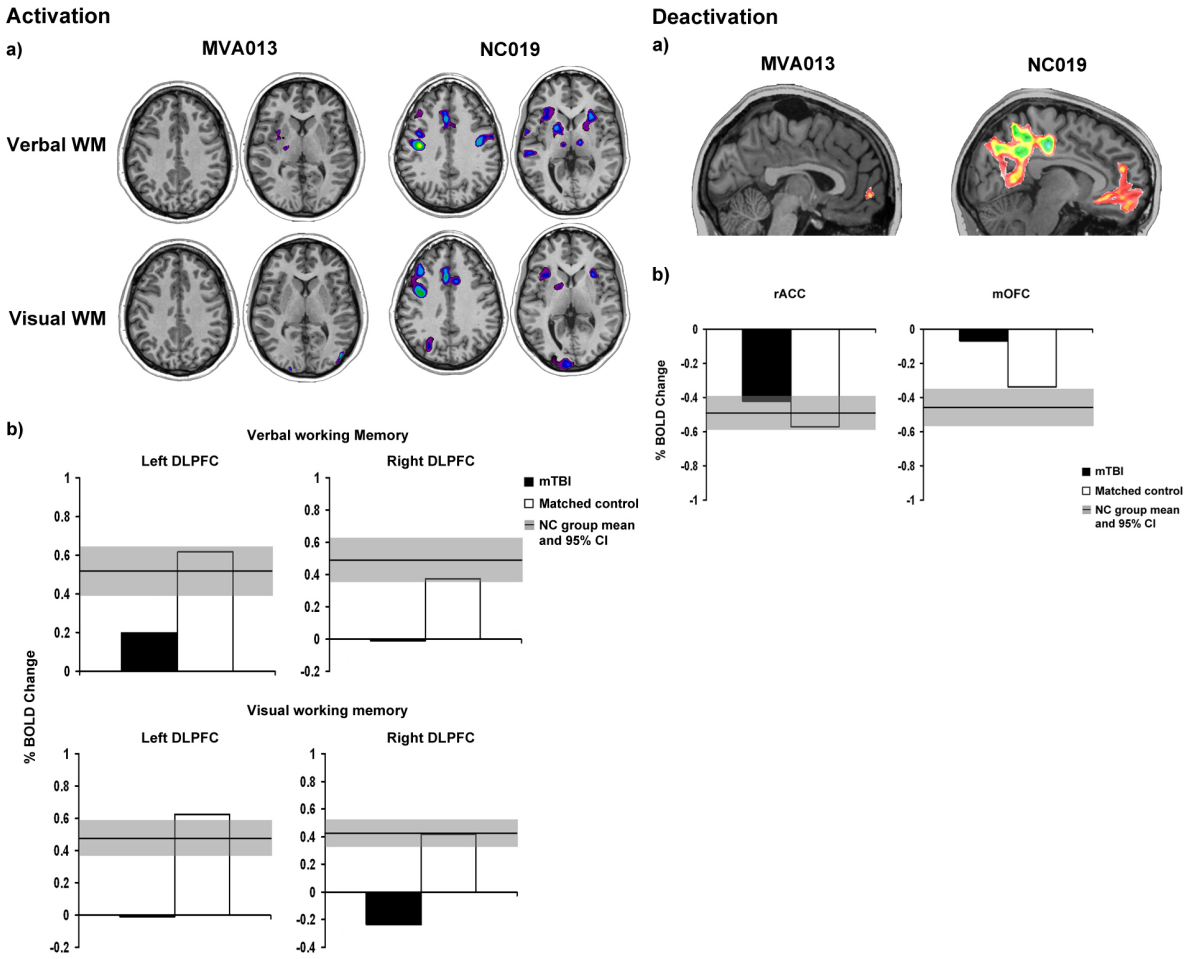


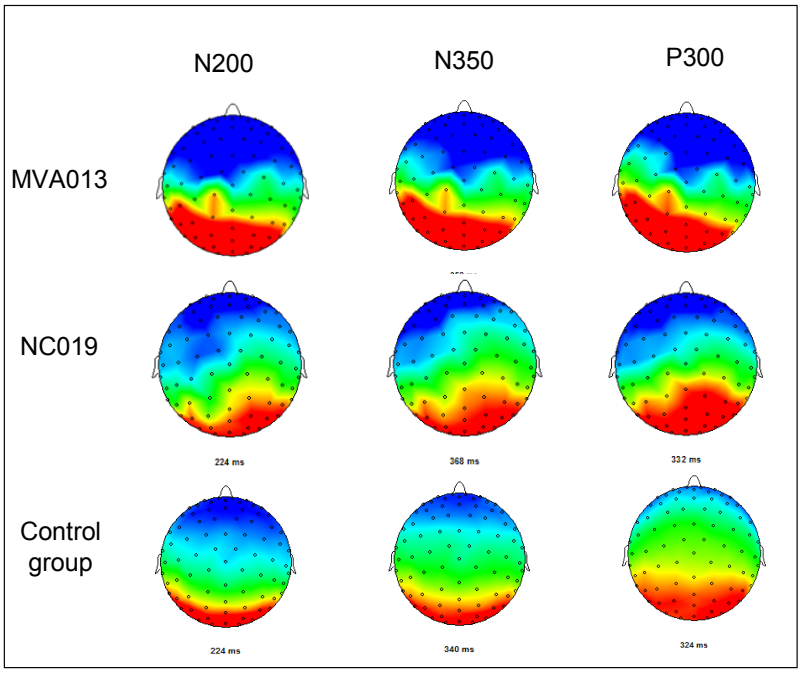
Figure 23: fMRI for MVA 013 vs NC 019

Behavioural data

MVA013
RT: 845.6 ms
Accuracy: 82.7%
PCS: n.a.

NC019
RT: 1121.6 ms
Accuracy: 96.7

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA013
Behavioural results: normal RT, normal accuracy
N200: normal amplitude, normal latency, normal distribution
N350: normal amplitude, normal latency, normal distribution
P300: normal amplitude, normal latency, normal distribution **(but left)**

Figure 24: ERP results : MVA013 vs NC019

4.2.9 MVA014 vs. NC016:

MVA014 had a very high PCS score (107) at the time of the study. Consistent with her symptom reporting, she did not show significant task-related brain activities in any of the prefrontal and subcortical ROIs during performance of both verbal and non-verbal working memory tasks. MVA014 also had a high BDI score (42) and she showed reduced deactivation in the medial prefrontal region (**Figure 25)**. Quantitative analyses further confirmed that all ROIs in this subject were significantly lower than the norm established with the control subject data. The result for the navigation task was more encouraging as significant activations were found in the retrosplenial cortex and the posterior parahippocampal gyri, except the activation peak in the right parahippocampus was relatively weak. Her neuropsychological profile showed difficulty with the immediate and delayed recalls of complex visuospatial material as well as sequential tapping with the left hand.

Her matched control NC016 showed activations in most of the primary ROIs. For the verbal working memory, significant peaks were found in bilateral dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex, bilateral caudate nucleus and left thalamus. For non-verbal working memory, significant activations were found in bilateral dorsolateral prefrontal cortex, bilateral ventrolateral prefrontal cortex, bilateral caudate nucleus and left thalamus. MVA016 also showed significant deactivation in the rostral cingulate cortex and medial orbitofrontal cortex. It is noted, however, that the magnitude of activation in the right DLPFC and of deactivation in the mOFC were smaller than the norm established using the control group data. Finally, her fMRI result for the navigation task showed the expected pattern of activation in the retrosplenial cortex

and the parahippocampal formation. Her neuropsychological profile was essentially normal except for slow sequential tapping with the left hand.

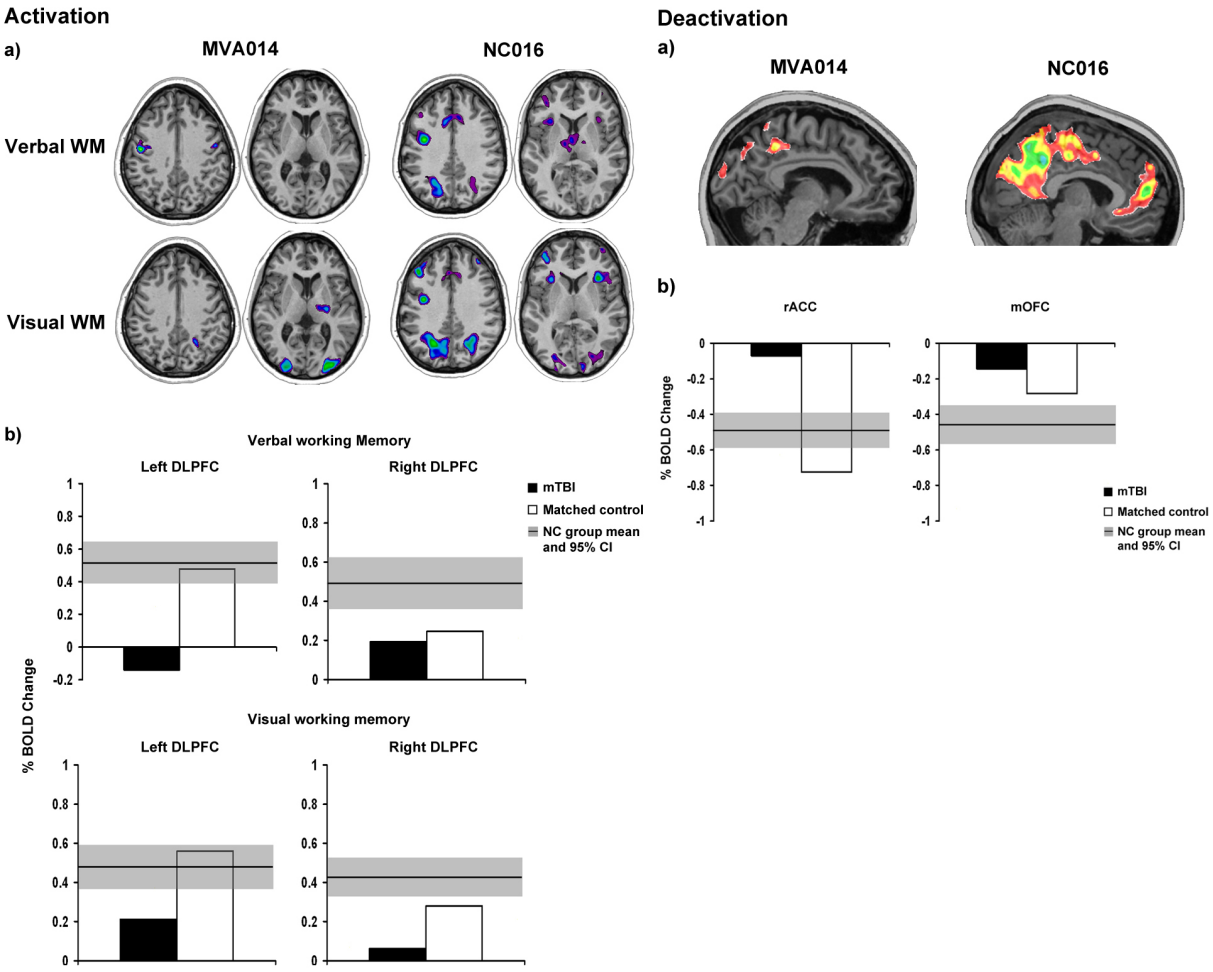


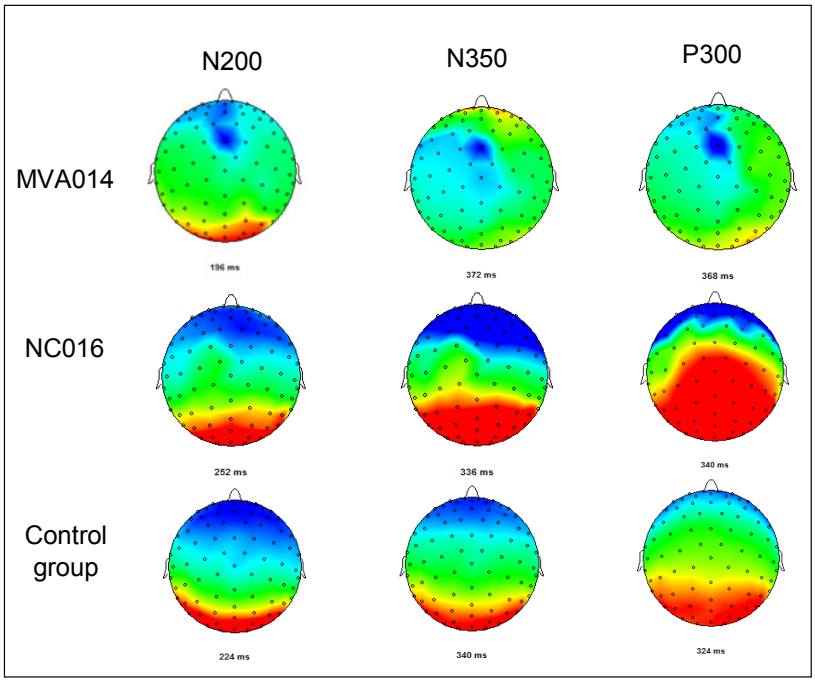
Figure 25: fMRI for MVA 014 vs NC 016

Behavioural data

MVA014
RT: 930.8ms
Accuracy: **51.3%**
PCS: n.a., but high

NC016
RT: 758.1 ms
Accuracy: 72%

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA014
Behavioural results: normal RT, **lower accuracy** (z score: -2.9)
N200: small amplitude, normal latency, **abnormal scalp distribution**
N350: small amplitude, normal latency, **abnormal scalp distribution**
P300: absent

Figure 26: ERP results : MVA014 vs NC016

4.2.10 MVA015 vs. NC020:

MVA015 reported moderate post-concussive symptoms (PCS score = 67). Consistent with her symptom reporting, her fMRI showed atypical activation patterns. For verbal working memory, significant activations were found in some of the primary ROIs, including the right ventrolateral prefrontal cortex and the left caudate nucleus. No activation was detected in DLPFC, which is crucial for working memory. For visual working memory, no activation was detected in any of the primary ROIs. Quantitative analyses indicated that the magnitudes of activations in DLPFC were below the norms (**Figure 27**). MVA015 also reported moderate symptoms of depression (BDI score = 18). This was reflected in her deactivation patterns in the rostral cingulate cortex and medial orbitofrontal cortex. As illustrated in **Figure 27**, the magnitudes of her deactivations in these areas were significantly lower than the norm. The functional MRI result for the navigation task also showed atypical results. MVA015 had significant but less robust activation in the retrosplenial cortex. There was a strong activation in the right parahippocampal gyrus but not in the left parahippocampal gyrus. Her neuropsychological profile showed slow learning and poor recall of verbal and complex visuospatial material, high sensitivity to interference, slow planning and difficulty with uni and bimanual sequential tapping.

NC020's fMRI result for the verbal task was comparable to that of the healthy control group as significant activations were detected in all primary ROIs. For visual working memory, NC020 showed significant prefrontal activations but failed to activate subcortical ROIs, except for sub-threshold activations in the thalamus. The pattern of deactivation of NC020 appeared normal as significant negative peaks were found in the rostral cingulate cortex and medial orbitofrontal

cortex. Finally the functional MRI result for the navigation task showed the expected activation pattern. Her neuropsychological profile showed difficulty with the immediate and delayed recalls of complex visuospatial material.

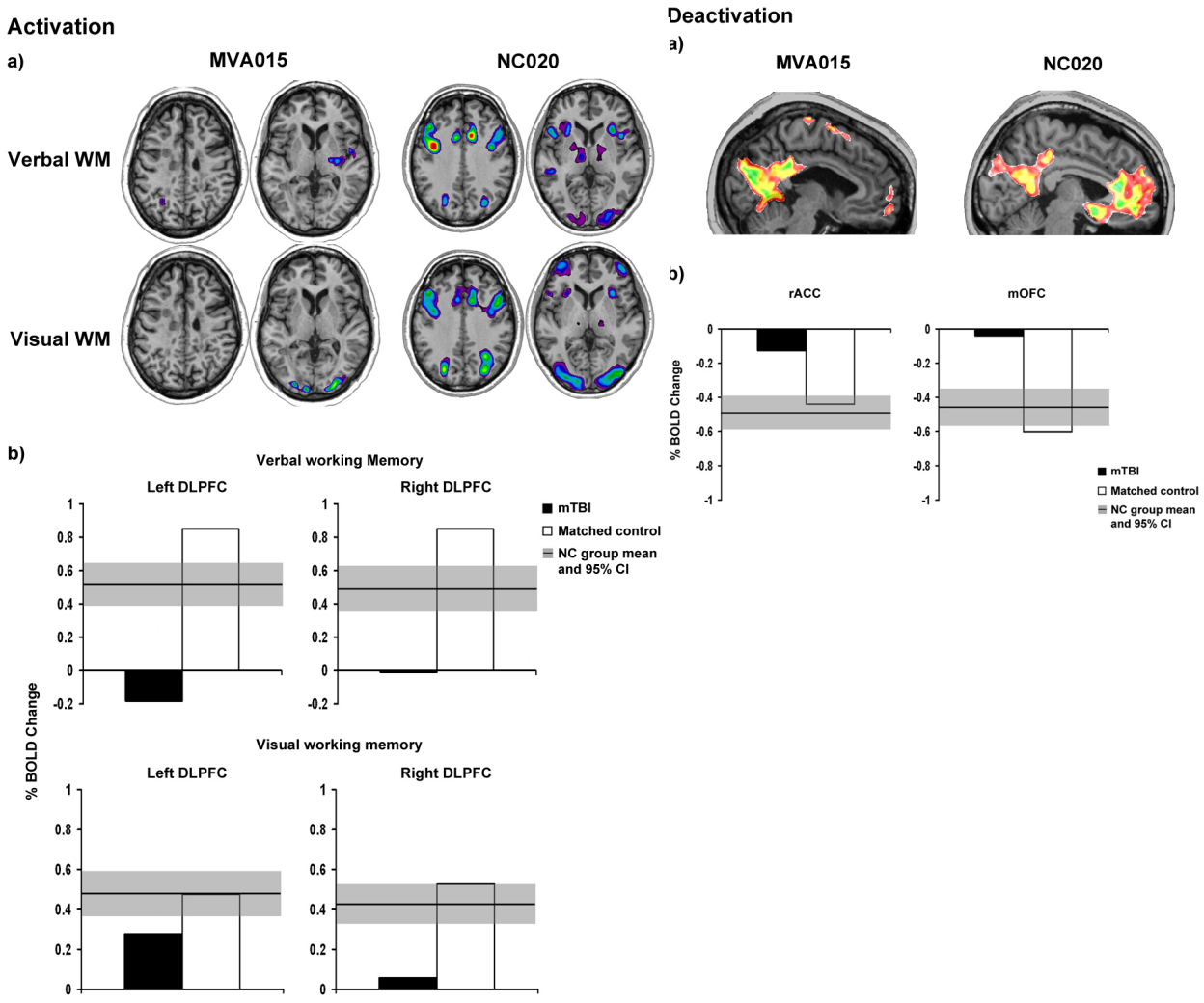
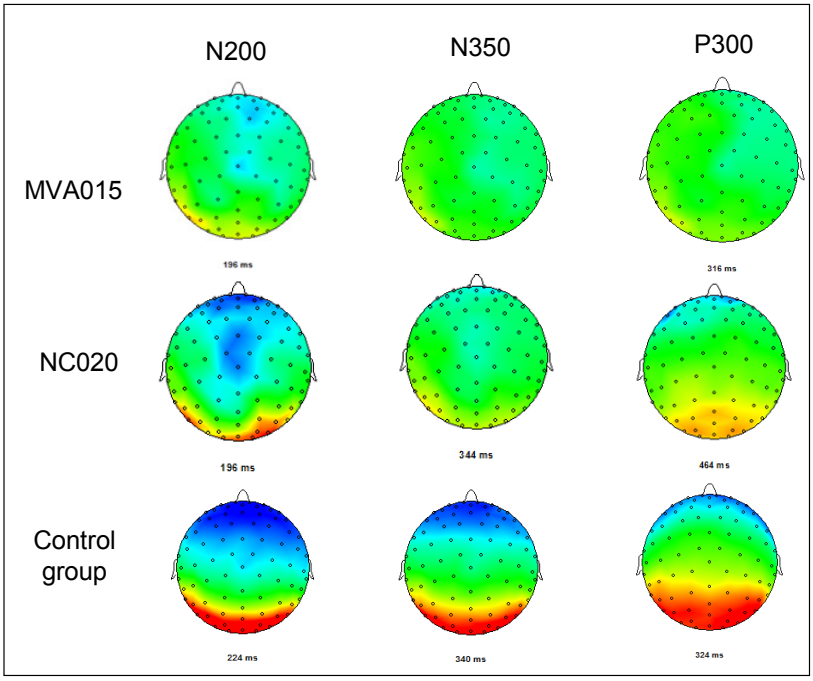


Figure 27: fMRI for MVA 015 vs NC 020

Figure 28: ERP for MVA015 (MTBI) vs NC020 (control)



Behavioural data

MVA015
RT: 1315.6 ms
Accuracy: **45.3%**
PCS: 67

NC020
RT: 1327.5 ms
Accuracy: 100 %

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%

Major findings for MVA015
Behavioural results: normal RT, **lower accuracy** (z score: -3.4)
N200: small amplitude, normal latency, normal distribution
N350: absent
P300: absent

Figure 28: ERP results : MVA015 vs NC020

4.2.11 MVA021 vs. NC026:

MVA021 has a relatively low PCS score (19). Consistent with her low symptom reporting, her fMRI results for both verbal and visual tasks showed significant bilateral activations in the DLPFC. Quantitative analyses revealed that, except in the left DLPFC for the verbal task, the magnitudes of all her prefrontal activations were within the norms (**Figure 29**). Nevertheless the pattern of her activation was still less than optimal as no significant peak was detected in other primary ROIs, including the ventrolateral prefrontal cortex, the caudate nucleus and the thalamus. MVA021 reported mild symptom of depression (BDI score = 16), and like healthy controls, MVA021 showed significant deactivation in the rostral cingulate cortex and medial orbitofrontal cortex (**Figure 29**). Her result for the navigation task also appeared normal with significant task-related activations in the retrosplenial cortex and the parahippocampal gyrus. Her neuropsychological profile showed slow planning and reduced sequential tapping with the right hand.

NC026's fMRI results were rather atypical for a healthy subject. She did not show significant activation in any of the primary ROIs. Sub-threshold activation peaks were detected only in the DLPFC bilaterally during the verbal task and in the right thalamus during the visual task. Furthermore, her deactivation in the rostral cingulate and medial orbitofrontal cortices were also attenuated. Atypical fMRI findings were also noted during the navigation task. Significant task-related activations were detected only in the left retrosplenial cortex and the left hippocampus, compared to the bilateral activation pattern typically seen in the control group. Furthermore, no

activation was detected in the posterior parahippocampal region that is known to be crucial in spatial navigation.

Her neuropsychological profile showed poor immediate and delayed recalls of complex visuospatial material, low mental flexibility and slow sequential tapping.

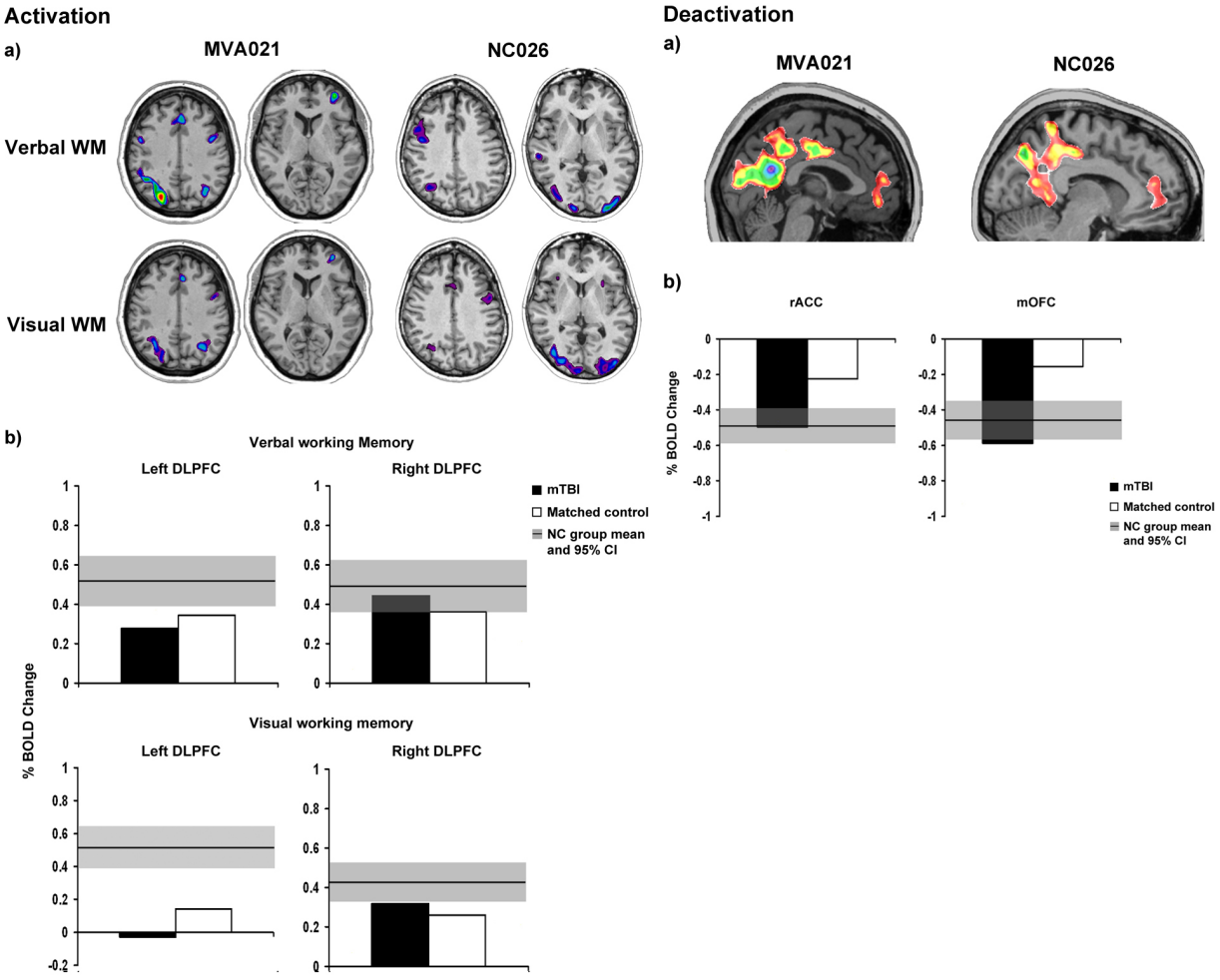


Figure 29: fMRI for MVA 021 vs NC 026

Figure 30: ERP for MVA021 (MTBI) vs NC026

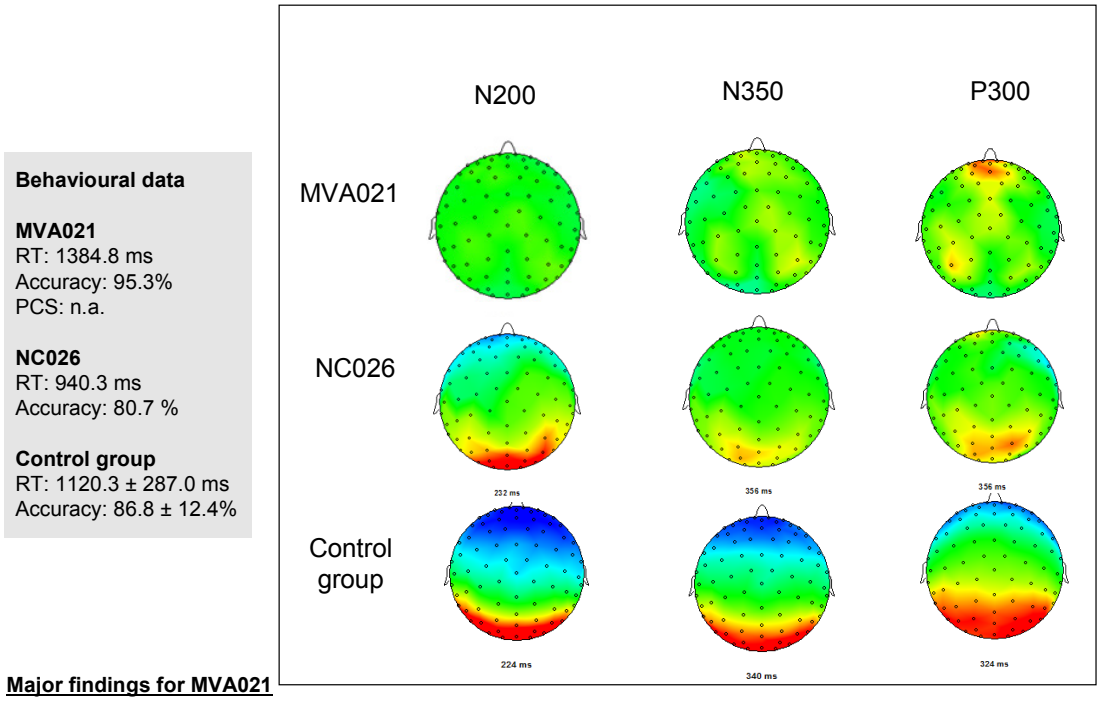


Figure 30: ERP results : MVA021 vs NC026

4.2.12 MVA022 (This participant does not yet have a matched control)

MVA022 has a moderate PCS score (55). His functional MRI results for verbal and visual working memory showed significant bilateral activations in the dorsolateral prefrontal cortex, a key cortical area for working memory. Quantitative analyses revealed that the magnitudes of his activations were within the norms (**Figure 31**). However, no activation was detected in other primary regions of interest (ROIs), including the ventrolateral prefrontal cortex, the caudate nucleus and the thalamus. This subject reported mild symptom of depression (BDI score = 12), and he showed hyperactivation in the rostral cingulate cortex, while the deactivation pattern in the medial orbitofrontal cortex was within the norm (**Figure 31**). Finally his result for the navigation task appeared atypical. Significant task-related activation was found in the retrosplenial cortex but key parahippocampal region failed to show robust activation.

Her neuropsychological profile showed high sensitivity to interference and slow sequential tapping aptitude.

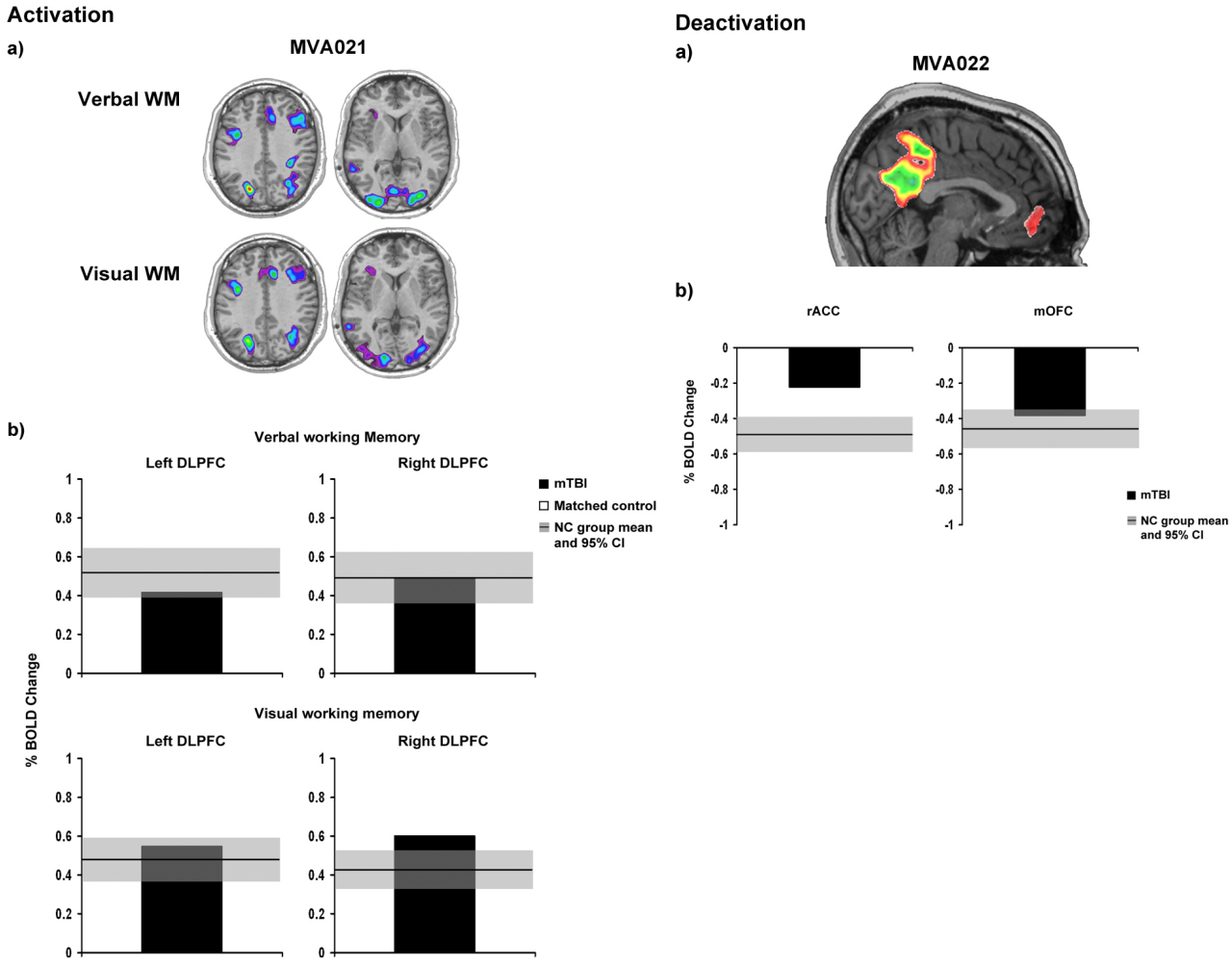


Figure 31: fMRI for MVA 022

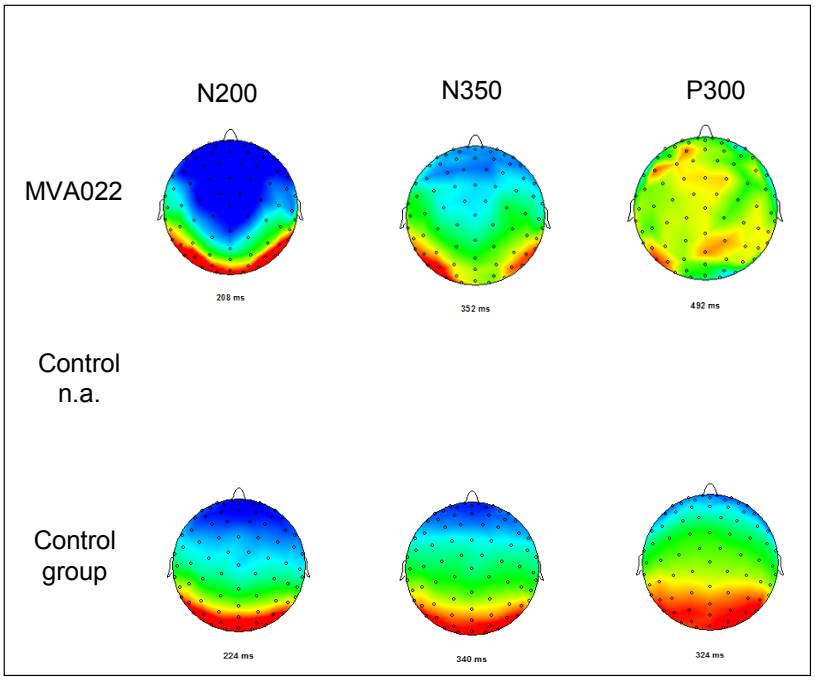
Figure 32: ERP for MVA022 (MTBI) vs no control

Behavioural data

MVA022
RT: 717.32 ms
Accuracy: 81.3%
PCS: ?

Control subject
RT: na
Accuracy: na

Control group
RT: 1120.3 ± 287.0 ms
Accuracy: 86.8 ± 12.4%



Major findings for MVA022
Behavioural results: normal RT, normal accuracy
N200: normal amplitude, normal latency, normal distribution
N350: normal amplitude, normal latency, normal distribution
P300: normal amplitude, **delayed latency** , normal distribution **(except a peak in the left parietal hemisphere)**

Figure 32: ERP results : MVA022 vs no control

5 Summary

All motor vehicle accident victims (MVAs) and control participants were matched for age, gender, and education; although an independent Mann-Whitney U-test showed significant differences in education between the groups ($p > .05$). Twenty-one participants were right handed; 2 (MVAs) were left handed. Of the MVA's, positions in the car included: driver position (8/12); co-driver position (1/12), back seat (2/12), no information (1/12). Seatbelt: yes (9/12), no (2/12), missing information (1/12). Type of impact: frontal impact (5/12), posterior impact (4/12), lateral impact (1/12), car flipping & spinning (3/12), multiple impacts (3/12). Mean velocity 66.82 km/h (SD = 39.89). Loss of consciousness: yes for several minutes (6/12), yes for several hours (coma induced, 2/12), no (4/12). Confusion/Disorientation: yes (10/12), no information (2/12). Retrograde amnesia: yes (4/12), no (8/12). Anterograde amnesia: yes (3/12), no (9/12).

Neuropsychological Evaluation: PCS is certainly the most notable deficit demonstrated by almost all patients; followed by depression and then anxiety. The majority of patients show at least one motor deficit while the rest of their profile is mixed underlining differential effects on cognitive functions. This underscores the necessity of administering a comprehensive battery of neuropsychological tests as difficulties may be bypassed with a reduced set of tests. It is noteworthy that there are no verbal memory deficits while the majority of MVA subjects showed problems with at least one visuospatial memory task.

fMRI: Functional magnetic resonance imaging results for the MVA group showed the following activation/deactivation patterns: Verbal working memory task: 10/12 showed hypoactivation in the left DLPFC and 7/12 in the right DLPFC; Visual working memory task: 7/12 showed hypoactivation in the left DLPFC and 11/12 in the right DLPFC; Depression: 4/12 showed reduced deactivation in the rACC and mOFC

Our findings so far are, in general, consistent with what we would expect based on our previous work. That is, the presence and the severity of PCS are associated with reduced BOLD activation in DLPFC. Similarly, the presence and severity of symptoms of depression are associated with reduced deactivation in rACC and mOFC. Unexpected findings were noted in certain subjects who reported significant symptoms of depression. In these cases, the subjects reported taking medication at the time of the study, which might have influenced the fMRI outcome. Atypical findings were also noted in 3 healthy subjects whose activation magnitudes were lower than expected. These findings highlight the importance of building a solid normal control database with a reliable sample size in order to establish the normal range of brain activation magnitude in the regions of interests.

EEG/ERP: A clear group difference was observed for the attentional component of the ERP, i.e. the P300. MTBI subjects had lower P300 amplitudes than the control subjects. This reduction in ERP amplitude suggests attentional dysfunctions. A smaller N350 in the MTBI group was also observed. It should also be noted that the MTBI subjects obtained quasi normal behavioural results with a trend towards lower accuracy suggesting use of compensatory mechanisms.

Table 26: Overview of demographics and neuropsychology

Table 25-1: Overview: Table showing demographics and neuropsychology-, EEG-, and fMRI individual and group results (L=left; R=right; n.s. = not significant; sign.= clinically significant; n/a = sign.=significant)

	DEMOGRAPHICS											
Subject	**Age**	**Gender**	**Handed-ness**	**Years of Education**	**Place in Car**	**Seatbelt**	**Type of Impact**	**Velocity in km/h**	**LOC**	**Confusion/ Disorientation**	**Post traumatic Amnesia**	
											Retrograde	**Anterograde**
PATIENTS (MVA)												
MVA001	29	male	right	18	driver	yes	posterior	stationary, the other 60	no	no info	no	no
MVA002	56	male	right	9	no info	no info	frontal	no info	yes	no info	yes	no
MVA003	32	female	right	14	driver	yes	lateral	20	yes	yes	yes	yes
MVA004	49	male	right	12	back seat	no	posterior, spinning	90	yes	yes	no	no
MVA005	35	male	right	11	driver	yes	frontal	80-90	no	yes	no	no
MVA011	21	female	right	15	back seat	yes	flipped	110	yes	yes	yes	yes
MVA012	20	male	left	13	driver	yes	flipped	110-120	yes	yes	no	no
MVA013	19	female	right	11	co-driver seat	yes	frontal	30-40, the other 80	no	yes	no	no
MVA014	22	female	right	12	driver	yes	Frontal, posterior	80	yes	yes	no	no
MVA015	37	female	right	12	driver	yes	Posterior	50-60, the other 90-110	yes	yes	no	no
MVA021	50	female	left	16	driver	no	posterior, frontal	30-40	no	yes	no	no
MVA022	24	male	right	8	driver	yes	frontal	100-120	yes	yes	yes	yes
CONTROLS (NC)												
MVA006	37	male	right	16	n/a	no	n/a	n/a	no	no	no	no
MVA007	30	male	right	14	n/a	no	n/a	n/a	no	no	no	no
MVA008	50	male	right	16	n/a	no	n/a	n/a	no	no	no	no
MVA009	54	male	right	16	n/a	no	n/a	n/a	no	no	no	no
MVA010	34	female	right	15	n/a	no	n/a	n/a	no	no	no	no
MVA016	20	female	right	15	n/a	no	n/a	n/a	no	no	no	no
MVA017	21	male	right	13	n/a	no	n/a	n/a	no	no	no	no
MVA018	21	female	right	14	n/a	no	n/a	n/a	no	no	no	no
MVA019	19	female	right	12	n/a	no	n/a	n/a	no	no	no	no
MVA020	37	female	right	17	n/a	no	n/a	n/a	no	no	no	no
MVA026	51	female	right	16	n/a	no	n/a	n/a	no	no	no	no
Group: PATIENTS (MVA) vs. CONTROLS (NC)												
	n.s.	matched	21 right/ 2 MVAs left	sign. NC > MVA	8/12 driver 1/12 codriver 2/12 backsat 1/12 no info	9/12 yes 2/12 no 1/12 no info	5/12 frontal 4/12 posterior 1/12 lateral 3/12 flip & spin 3/12 multiple	Mean 66.82 km/h SD = 39.89	8/12 yes 4/12 no * artificial coma	10/12 yes 2 no info	4/12 yes 8/12 no	3/12 yes 9/12 no

Table 25: Overview of demographics and neuropsychology

Table 25-2: Overview: Table showing demographics and neuropsychology-, EEG-, and fMRI individual and group results (Sup. = superior, High Avg. = high average; Avg. = average; Low Avg. = low average; Imp. = impaired; n.s. = not significant; sign.= clinically significant)

Subject	Mailing ording	Symptoms/Mood					NEUROPSYCHOLOGICAL EVALUATION									Motor
		Post Concussion		Depression		Anxiety	General Cognitive Functioning			Verbal Fluency	Memory		Higher Cognitive Functioning			
							General	Verbal	Performance		Verbal	Visual	Problem Solving	Mental Switchi ng	Mental Inhibitio n	
PATIENTS (MVA)																
MVA001	n.s.	62	severe	26	moderate	14	normal	avg.	avg.	avg.	imp.	normal	imp.	imp.	normal	imp.	imp.
MVA002	n.s.	20	mild	5	normal	3	normal	high avg.	high avg.	high avg.	imp.	normal	imp.	normal	normal	normal	imp.
MVA003	n.s.	102	severe	39	severe	35	severe	avg.	avg.	avg.	normal	normal	imp.	imp.	imp.	imp.	normal
MVA004	n.s.	77	severe	32	severe	22	severe	avg.	avg.	avg.	imp.	imp.	imp.	imp.	normal	imp.	imp.
MVA005	n.s.	100	severe	25	moderate	18	severe	avg.	avg.	avg.	imp.	normal	normal	normal	normal	normal	imp.
MVA011	n.s.	57	severe	12	normal	12	normal	avg.	avg.	avg.	normal	normal	normal	normal	normal	normal	imp.
MVA012	n.s.	24	mild	3	normal	3	normal	high avg.	avg.	sup.	normal	normal	normal	normal	normal	normal	imp.
MVA013	n.s.	65	severe	24	moderate	21	mild	avg.	avg.	high avg.	normal	normal	normal	normal	normal	normal	normal
MVA014	n.s.	107	severe	16	mild	28	modera te	avg.	avg.	avg.	normal	normal	imp.	normal	normal	normal	normal
MVA015	n.s.	67	severe	5	normal	5	normal	avg.	avg.	avg.	normal	imp.	imp.	normal	imp.	normal	imp.
MVA021	n.s.	55	severe	19	mild	16	normal	avg.	avg.	avg.	normal	normal	normal	imp.	normal	normal	normal
MVA022	n.s.	51	severe	12	normal	12	normal	avg.	avg.	avg.	normal	normal	normal	normal	imp.	normal	normal
CONTROLS (NC)																
MVA006	n.s.	0	normal	0	normal	5	normal	high avg.	avg.	sup.	normal	normal	normal	normal	normal	normal	normal
MVA007	n.s.	2	normal	0	normal	3	normal	sup.	sup.	high avg.	normal	normal	normal	imp.	normal	normal	normal
MVA008	n.s.	8	normal	3	normal	0	normal	avg.	avg.	avg.	normal	normal	normal	imp.	normal	normal	normal
MVA009	n.s.	0	normal	7	normal	4	normal	sup.	sup.	high avg.	normal	normal	normal	normal	normal	normal	imp.
MVA010	n.s.	5	normal	6	normal	10	normal	high avg.	avg.	high avg.	normal	normal	normal	normal	normal	normal	normal
MVA016	n.s.	5	normal	0	normal	4	normal	sup.	sup.	sup.	normal	normal	normal	normal	normal	normal	imp.
MVA017	n.s.	8	normal	1	normal	7	normal	sup.	sup.	high avg.	normal	normal	normal	normal	normal	normal	normal
MVA018	n.s.	15	normal	20	mild	26	mild	high avg.	high avg.	avg.	normal	normal	normal	normal	normal	normal	normal
MVA019	n.s.	12	normal	3	normal	11	normal	sup.	sup.	avg.	normal	normal	normal	normal	normal	normal	normal
MVA020	n.s.	2	normal	0	normal	2	normal	sup.	sup.	high avg.	normal	normal	normal	imp.	normal	normal	normal
MVA026	n.s.	18	mild	3	normal	9	normal	avg.	avg.	low avg.	normal	normal	normal	normal	imp.	imp.	normal
Group: PATIENTS (MVA) vs. CONTROLS (NC)																
	n.s.	sign.	MVA > NC	sign.	MVA > NC	sign.	MVA > NC	sign.	sign.	n.s.	sign.		n.s.	n.s.	n.s.	n.s.	sign.

Table 27: Overview of demographics and neuropsychology

Table 25-3: Overview: Table showing demographics and neuropsychology-, EEG-, and fMRI individual and group results (hyper = hyper activation; hypo = hypo activation; n.s. = not significant; sign.= clinically significant)

	EEG - Visual Working Memory					fMRI - Activation				fMRI - Deactivation	
						Verbal Working Memory		Visual Working Memory			
Subject	**Accuracy**	**RT**	**N200**	**N350**	**P300**	**L DLPFC**	**R DLPFC**	**L DLPFC**	**R DLPFC**	**rACC**	**mOFC**
PATIENTS (MVA)											
MVA001	normal	abnormal	normal	abnormal	abnormal/absent	hypo	hypo	normal	hypo	hyper	hyper
MVA002	normal	normal	normal	normal	normal	hypo	hypo	normal	hypo	normal	normal
MVA003	normal	normal	normal	normal	normal	normal	hypo	normal	hypo	normal	normal
MVA004	abnormal	normal	normal	normal	abnormal/absent	hypo	normal	normal	hypo	normal	normal
MVA005	normal	normal	abnormal	normal	abnormal/absent	hypo	normal	hypo	hypo	normal	normal
MVA011	abnormal	normal	normal	normal	normal	hypo	hypo	hypo	hypo	hyper	hyper
MVA012	aretefact	aretefact	aretefact	aretefact	aretefact	normal	normal	normal	normal	normal	normal
MVA013	normal	normal	normal	normal	normal	hypo	hypo	hypo	hypo	normal	hyper
MVA014	abnormal	normal	normal	abnormal	abnormal/absent	hypo	hypo	hypo	hypo	hyper	hyper
MVA015	abnormal	normal	abnormal	abnormal	abnormal/absent	hypo	hypo	hypo	hypo	hyper	hyper
MVA021	normal	normal	abnormal	abnormal	abnormal/absent	hypo	normal	hypo	hypo	normal	normal
MVA022	normal	normal	normal	normal	normal	hypo	normal	hypo	hypo	hyper	normal
CONTROLS (NC)											
MVA006	normal	normal	normal	normal	normal	hypo	normal	normal	normal	normal	normal
MVA007	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal
MVA008	normal	normal	normal	normal	normal	normal	hypo	normal	normal	normal	normal
MVA009	normal	abnormal	normal	normal	normal	normal	normal	normal	normal	normal	normal
MVA010	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal
MVA016	normal	normal	abnormal	normal	normal	normal	hypo	normal	hypo	normal	hyper
MVA017	abnormal	normal	normal	normal	abnormal	hypo	normal	normal	normal	hyper	normal
MVA018	normal	normal	normal	normal	normal	normal	normal	hypo	normal	normal	normal
MVA019	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal	hyper
MVA020	normal	normal	normal	normal	abnormal	normal	normal	normal	normal	normal	normal
MVA026	normal	normal	normal	abnormal	normal	hypo	normal	hypo	hypo	hyper	hyper
Group: PATIENTS (MVA) vs. CONTROLS (NC)											
	n.s.	n.s.	n.s.	n.s.	t(20)=-2.53, p=0.02	hypo	hypo	hypo	hypo	normal	normal

6 Significance

Conventional clinical neuroimaging of the brain, including MRI, is often interpreted as "normal" in persons with mild traumatic brain injury. A normal MRI of the brain after a mild traumatic brain injury does not suggest the absence of injury but instead indicates only that any changes in the brain caused by the traumatic brain injury are below the detection threshold of conventional clinical MRI. The present study shows that postconcussive symptoms (PCS) are associated with cognitive dysfunctions that vary among individuals and this underscores the necessity of using an exhaustive neuropsychological test battery. The presence and severity of PCS, including depression, are associated with altered patterns in frontal, parietal and hippocampal regions identified with event-related potentials (ERP) and functional neuroimaging (fMRI). Because conventional neuroimaging (e.g. CT, MRI) does not allow identification of the dysfunctional regions, the evaluation of the severity of the PCS, including depression and anxiety, is primordial as it appears to have a pathological basis and has implications for diagnosis, treatment, and rehabilitation. Our approach, using neuropsychological testing, fMRI and ERP, holds great potential for identifying in soldiers the presence of suspected cerebral dysfunctions following traumatic brain injury, particularly following blast exposure. Future plans: Ideally, soldiers could be tested with these techniques prior to leaving for missions, so as to obtain baseline data on each one. Alternatively, those who return from combat with post-concussion symptoms could be tested with these techniques and the results to be compared to our group data of normal control subjects that are comparable in age

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Glossary

DTI – diffusion tensor imaging

EEG – electroencephalography

FLAIR – fluid-attenuated inversion recovery

fMRI – functional magnetic resonance imaging

MRI – magnetic resonance imaging

mTBI – mild traumatic brain injury

PCS – Post concussive symptoms

TBI – traumatic brain injury

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(U) Introduction: In the Canadian Forces (CF), injuries involving impact of the head within an enclosed space (a vehicle) are common and the possibility of cortical impact injuries in such cases is quite high. While conventional neuroimaging techniques may show normal results, cognitive problems are frequently reported by people who have sustained cortical impact or traumatic brain injury. In order to develop a comprehensive clinical diagnosis for return soldiers that might experience signs and symptoms of possible brain injury due to cortical impact, the present study aimed to compare motor vehicle accident (MVA) victims where cortical impact is prevalent to an age matched control group. All MVA victims were investigated using carefully selected neuroimaging and electrophysiological procedures together with a validated neurocognitive test battery. Results: 1) at the neuropsychological level, postconcussive symptoms (PCS) were the most notable complaints expressed by almost all patients; followed by symptoms of depression and anxiety. The majority of patients showed at least one motor deficit while the rest of their profile was mixed underlining differential effects on cognitive functions. There were no verbal memory deficits while the majority of MVA subjects showed problems with at least one visuospatial memory task; 2) with functional magnetic resonance imaging the results were consistent with our previous work. The presence and severity of PCS were associated with reduced BOLD activation in dorsolateral prefrontal cortex (DLPFC). Similarly, the presence and severity of symptoms of depression were associated with reduced deactivation in rostral anterior cingulate cortec (rACC) and medial orbitofrontal cortex (mOFC). This pattern is in line with the fact that those depressed subjects who did not show this profile were on antidepressant medication at the time of the study. Atypical findings were also noted in three healthy subjects highlighting the importance of building a solid normal control database with a reliable sample size in order to establish the normal range of brain activation magnitude in the regions of interests; 3) with event–related potentials (ERP), MVA victims presented lower P300 amplitudes and a smaller N350 than the control subjects, in keeping with the presence of attentional dysfunctions. In addition, quasi normal behavioural results in the MVA group was observed suggesting use of cerebral compensatory mechanisms by that group. Conclusion: In MVA victims, PCS are associated with cognitive dysfunctions that vary among individuals and this underscores the necessity of using an exhaustive neuropsychological test battery with this population. PCS appear to have a pathological basis as they are associated with cerebral dysfunctions, particularly in frontal, parietal, and hippocampal regions, identified with event–related potentials and functional neuroimaging. As conventional neuroimaging (e.g. CT, MRI) does not allow identification of dysfunctional regions, the evaluation of the severity of PCS, including depression and anxiety, following a MVA is primordial as it has implications for diagnosis, treatment, and rehabilitation. Our approach, using neuropsychological testing, fMRI and ERP, holds great potential for identifying the presence of suspected cerebral dysfunctions in soldiers following traumatic brain injury, particularly in blast exposure.

(U) Introduction: Au sein des Forces Armées Canadiennes, les blessures impliquant un impact à la tête dans un environnement restreint comme celui dans un véhicule motorisé sont communes et la possibilité que les passagers y subissent un traumatisme crânio–cérébral (TCC) est très élevée. Alors que les méthodes conventionnelles d'imagerie cérébrale montrent habituellement des résultats normaux, des problèmes cognitifs sont souvent rapportés par les victimes de TCC. Afin de développer une batterie clinique diagnostique

applicable aux soldats se plaignant de symptômes laissant présager la présence d'un TCC suite à une exposition à une explosion, la présente étude visait à comparer des accidentés de la route chez qui un TCC prévaut à un groupe témoin pairé selon l'âge. Tous les sujets TCC ont été soumis à une batterie de tests neuropsychologiques, d'imagerie cérébrale fonctionnelle et électrophysiologiques. Résultats: 1) au plan neuropsychologique, les symptômes post–commotionnels (SPC) prévalaient chez les sujets TCC suivis de symptômes de dépression et d'anxiété. La majorité des patients ont montré au moins un déficit moteur alors que le reste de leur profil était mixte soulignant des effets différentiels sur le fonctionnement cognitif. Aucun déficit des fonctions verbales n'a été constaté mais la majorité des TCC ont montré des difficultés lors d'au moins une tâche de mémoire visuelle. 2) avec la résonance magnétique fonctionnelle, les résultats étaient généralement en accord avec ceux obtenus lors de nos études précédentes. La présence et la sévérité des SPC étaient associées avec un signal en oxygénation sanguine (BOLD) réduit dans le cortex dorso latéral préfrontal. De façon analogue, la présence et la sévérité des symptômes dépressifs étaient associées avec une désactivation réduite dans le cortex cingulaire antérieur rostral et dans le cortex orbitofrontal médian. Ces résultats s'enlignent avec le fait que les sujets se plaignant de symptômes dépressifs ne montrant pas ce patron d'activation prenaient de la médication antidépressive au moment de l'étude. Des résultats atypiques ont également été obtenus par trois sujets témoins, ce qui souligne l'importance de cumuler des données normatives solides avec un échantillonnage fiable. 3) avec les potentiels évoqués, les TCC ont montré des amplitudes réduites des ondes P300 et N350 par rapport aux sujets témoins, en accord avec la présence de dysfonctions attentionnelles chez le groupe TCC. De plus, les performances comportementales quasi normales observées chez les TCC laissent croire à l'utilisation de mécanismes cérébraux compensatoires par ce groupe. Conclusions : Chez les TCC, les SPC sont associés à des dysfonctions cognitives variables selon les individus et ceci souligne la nécessité d'utiliser une batterie neuropsychologique exhaustive chez cette population. Les SPC semblent avoir une pathologie sous–jacente car ils sont associés à des dysfonctions cérébrales touchant particulièrement les régions frontale, pariétale et hippocampique identifiées par l'imagerie cérébrale fonctionnelle et les potentiels évoqués. Étant donné que l'imagerie cérébrale conventionnelle (par ex. CT scan, IRM) ne permet pas d'identifier des régions dysfonctionnelles, l'évaluation de la sévérité des SPC, incluant la dépression et l'anxiété, à la suite d''un accident de la route ou à l'exposition à une explosion, revêt une importance primordiale à cause des implications qu'elle a pour le diagnostic, le traitement et la réadaptation. Notre approche utilisant la résonance magnétique fonctionnelle, l'évaluation neuropsychologique et les potentiels évoqués possède un potentiel considérable pour identifier la présence possible de dysfonctions cérébrales suite à un TCC particulièrement lors de l'exposition à une explosion

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(U) brain injury, MRI, EEG, cognition

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